Seizures in oligodendroglial tumors

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Practice points

- Changes of peritumoral tissue and microenvironment, alterations of glutamate metabolism and genetic factors as the IDH1 mutation play a role in tumor-related epilepsy.
- Monotherapy by levetiracetam or valproic acid are evidence-based choices as first anticonvulsants with good tolerability. If ineffective, their combination is successful in 60% of remaining patients.
- Surgery, radiotherapy, chemotherapy greatly helps in seizure control.
- Oligodendrogliomas show a high frequency of pharmacoresistant epilepsy. This can be countered by adjusting anticonvulsants with therapeutic drug monitoring, or by antitumor directed therapy.
- Brain tumor patients seem more vulnerable to the side effects of anticonvulsants, often involving the CNS by cognitive changes, the bone marrow or skin.

Epilepsy develops in more than 70–90% of oligodendroglial tumors and represents a favorable indicator for long-term survival if present as the first clinical sign. Presence of IDH1 mutation is frequently associated with seizures in oligodendrogliomas, next to alterations of glutamate and GABA metabolism in the origin of glioma-associated epilepsy. Treatment by surgery or radiotherapy results in seizure freedom in about two-thirds of patients, and chemotherapy to a seizure reduction in about 50%. Symptomatic anticonvulsive therapy with levetiracetam and valproic acid as monotherapy are both evidence-based drugs for the partial epilepsies, and their effective use in brain tumors is supported by a large amount of additional data. Pharmacoresistance against anticonvulsants is more prevalent among oligodendrogliomas, occurring in about 40% despite polytherapy with two anticonvulsants or more. Toxic signs of anticonvulsants in brain tumors involve cognition, bone marrow and skin. Previous neurosurgery, radiation therapy or chemotherapy add to the risks of cognitive dysfunction.

Management of seizures is an important part of the treatment of low- and high-grade gliomas as more than 70% of patients present with seizures. In this review, we will discuss issues related to seizures in gliomas, focusing on oligodendrogliomas. These include the underlying mechanisms of seizure development in brain tumors, clinical presentation by seizures, efficacy of antitumor therapy on seizure control, symptomatic management by antiepileptic drugs (AEDs), pharmacoresistance and drug–drug interactions. Seizures as the only clinical sign has prognostic value for duration of survival, and recurrence of seizures following a seizure-free interval may indicate tumor progression. Brain tumor patients are more prone to toxic effects of anticonvulsants than

KEYWORDS

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in general epilepsy, often related to CNS, bone marrow or skin.

Mechanisms of seizure development in gliomas

Low-grade glioma (LGG) brain tumors seem to have a stronger predilection for epileptogenesis than more malignant brain cancers. LGG frequently show seizures as the first clinical sign and are usually larger in size than glioblastomas (GBM) at the time of presentation. The latter present more frequently by focal neurological deficits while being smaller in volume [1,2]. In LGG a slower growth rate would favor development of seizure-prone changes like de-afferentation and disconnection of cortical areas leading to denervation hypersensitivity [3]. A more gradual evolution may permit adaptive changes of the surrounding brain tissue to occur. In this way, higher seizure frequency without neurological deficits may be explained despite a larger tumor volume. Brain tumors also affect the brain network distant to the original site leading to disruptions of functional connectivity in remote areas [4]. Alterations in micro-environment including hypoxia and acidosis will induce swelling and cell damage together with deregulation of sodium and calcium influx with generation of electrical impulses. Overexpression of voltage-gated sodium channels as well as changes of the SV2A synaptic vesicle protein associated with calcium accumulation may facilitate recurring generation of action potentials around tumor cells [5].

Molecular biological factors of seizure development

Genetics changes are also involved in epileptogenesis. In glioneuronal tumors, a mutation of the BRAF V600E is observed in about 50% of gangliogliomas. Presence of this mutation in combination with dysregulation of the mTOR pathway is associated with higher seizure frequency [6]. In LGG, one often observes mutations of codon 132 isocitrate-dehydrogenase 1 (IDH1) in 71–88% of grade II astrocytomas and oligodendrogliomas [7–10]. The IDH1 enzyme belongs to the Krebs citric-acid cycle catalyzing isocitrate into α -ketoglutarate. If mutated, 2-hydroxyglutarate will be formed instead. The latter resembles glutamate structurally and may activate NMDA receptors with ensuing epileptogenesis. Glutamate plays also a role in seizure

development. Abnormalities include increased expression of specific glutamate receptor subtypes, low activity of glutamine synthetase and almost absent intracellular uptake together with excessive extracellular glutamate levels [11,12]. Disturbances of chloride balance in gliomas are secondary to changes in chloride cotransporters by reduced KCC2 and increased NKCC1 expression with accompanying changes in GABA metabolism [13,14]. Glutamergic stimulation of NMDA- and AMPA-receptors may activate intracellular mTOR, AKT and MAPK signaling pathways leading both to cell growth as to epileptogenesis [15,16].

Seizures as presenting sign

Seizures are the most common presenting symptom in patients with LGG, and are determined by tumor subtype and hemispheric location. Neurogliomas (dysembryoblastic neuro-epithelial tumors and gangliogliomas) show an overall 80–100% seizure incidence, LGGs 60–85% and GBMs 40–60%. For each type of glioma, the appearance of seizures is usually the presenting clinical symptom, and for neuroglial tumors often the only clinical sign [17,18]. In oligodendrogliomas, frequency varies between 70 and 90%, and represents the first clinical symptom in 60% of cases or more [18–22]. They are associated with IDH1 mutations in 80–85% [17–21], epilepsy in LGG presents as simple partial seizures in 21–57%, complex partial in 7–31% and as secondary generalized seizures in 47–82% (Table 1). Patients with secondary generalized seizures more often show absence of LOH 19q [22]. Simple partial seizures are more difficult to control by use of anticonvulsants than other seizure types [23,24].

Tumor location & the risk on seizures

LGG are located in the frontal lobe in 50–70% of patients, in the temporal lobe in 18–37%, parietal lobe in 3.4–6% and 45% of tumors involve two lobes. Within these locations, LGG have a preference for secondary functional areas, including the supplementary motor area and insular cortex. Overall, oligodendroglial tumors more often involve the cortex with a higher risk on seizures as compared with astrocytomas, which tend to occur more often in the white matter tumors involving the frontal, temporal or parietal lobe as opposed to occipital or midline lesions. [11,23,25].

Prognosis of seizure & its relation to survival

Concerning seizure prognosis, number and duration of pre-operative seizures are an indicator of the risk on continuation of seizures following brain tumor surgery [17,23]. A gross total or subtotal resection (OR 16), surgery within <1 year after presentation (OR 1.9), successful seizure control by anticonvulsants (OR 2.1) are associated with a better postoperative seizure control [11,23,26,27].

In relation to longevity, patients with LGG presenting with seizures show a longer overall survival time (HR: 0.27) [21,28,29]. Conversely, neurological deficits or poor performance status at presentation are associated with worse longevity [26]. In oligodendrogliomas, the relation between seizures and survival shows remarkable characteristics as observed in the series of McDonald and Cairncross [21]. Besides that seizures as presenting symptom are related to longer survival, the subgroup of patients with only one single seizure before surgery (14% of all patients) do even better, showing a 90% survival at 10 years. In contrast, almost a third of the small subgroup of patients presenting with other neurological deficits (9.6% of all patients) die within 1 or 2 years. However, from the remaining patients in this subgroup all were alive at 10 years after diagnosis, resulting in 62% survival at 10 years in this subset. The largest group of oligodendrogliomas have either two or more or show relapsing seizures, and a steadily decreasing survival slope with 50% median survival at 10 years. Patients with refractory seizures tend to do worse than those with controlled seizures [21].

Presence of IDH1 mutation, codeletion of 1p and 19q, histology and frontal tumor location in WHO grade II oligodendroglial tumors count as positive prognostic feature for overall survival with or without presentation by seizures on uni- or multi-variate analysis [30–32]. Solitary 19q loss is associated with anaplastic tumors and temporal lobe location [31]. Obviously, presence of seizures, neurological deficits and performance status are interrelated. Thus, in multi-variate analysis, epilepsy is not always retained as prognostic factor for survival or when combined with the presence of IDH1 mutation [27,33]. Once postoperative seizure control has been achieved, a recurrence of seizures after more than 6 months of seizure freedom is a strong indicator of tumor progression in about 50% of patients of LGG and in two-thirds of patients with GBM [23,34].

Antitumor therapy

Antitumor directed treatment as surgical resection, radiotherapy and chemotherapy are increasingly recognized as effective tools contributing to seizure control.

• Surgery

Surgical resection is a crucial part of tumor therapy as well as being effective for seizure control. By removing the tumor, the surrounding cortex may lose its ability to initiate seizures and indeed more than two-thirds of patients become seizure free or have a meaningful improvement following surgical resection [23,35]. Large series in low-grade gliomas indicate an overall seizure-free rate of 67–87% [36–40]. Medically controlled seizures before surgery, presence of seizures for >1 year and gross-total resection contribute to postoperative seizure freedom [26]. Following a complete resection, 89% of patients become seizure-free at 6 months as compared with 57% following a subtotal resection in LGG (Table 2). In most studies, no distinction is made between grade II and III oligodendroglial tumors as to seizure response, although the most significant factor seems to be a complete resection. In case of pharmacoresistant seizures, performing a gross tumor surgery seems relatively more effective.

• Radiotherapy

Retrospective studies in low-grade gliomas indicate a 50% reduction in seizure frequency of 56–77% and a seizure-freedom of 38–80% [41–44]. A randomized EORTC Phase III trial on external radiotherapy in LGG to a cumulative dose of 65 Gy showed that 75% of patients became seizure-free following early and 59% following late application of radiation therapy [45] (Table 2). In medical intractable epilepsy in grade II gliomas, radiation therapy reduced seizure frequency in 76% of patients at 3 and at 12 months, even without distinct tumor response on MRI (Table 2) [43]. Similar percentages of 56–76% seizure freedom were found in the combined group of grade II and III gliomas [43]. Besides a direct antitumor effect, ionizing radiation might diminish seizure activity by damaging epileptogenic neurons or influencing the micro-environment around tumor.

• Chemotherapy

The efficacy of chemotherapy with alkylating agents for treating WHO grade II and III oligodendrogliomas and oligoastrocytomas,

Table 1. Seizure characteristics in low-grade gliomas.										
Characteristics	Nataf 2005 (n = 318)	Chang 2008 (n = 332)	Breemen 2009 (n = 33)	Huang 2011 (n = 103)	Mirsattari 2011 (n = 166)	Scheie 2011 (n = 95)	You 2012 (n = 508)	Pallud 2014 (n = 1509)	Koekkoek 2014 (n = 104)	Zhong 2015 (n = 311)
Glioma subtype (%)	OII 57.2	A: 38.8	A: 70.9	A: 34.0	ODII 64.5	ODII 62.1	A: 45.1	A: 21.7	A: 64.4	A: 45
	OIII 42.8	OD: 28.6	OD: 25.9	OD: 26.2	ODIII 35.5	ODIII 37.9	OD: 9.4	OD: 51.8	OD: 23.1	OD: 10
		OA: 32.8	OA: 9.7	OA: 39.8			OA: 45.5	OA: 18.6	OA: 12.5	OA: 45
Sz. at presentation (%)	OII 91.5	81	69.7	A: 68.6	75.3	61	A: 67.2		94.2	A: 70.7
	OIII 76			OD: 59.3			OD: 64.5			OD: 64.5
				OA: 75.6			OA: 71.4			OA: 72.9
Refractory sz. (%)		A: 28.8			ODII 44.0			37.2		
		OD: 30.3			ODIII 37.2					
		OA: 40.9								
Tumor location										
Frontal (%)	OII 47.3	54.8			60.8	63	70.9	50.3		
	OIII 57.4									
Temporal lobe (%)	OII 26.9	33.4		42.2	37.3	18	37.2	18.2		
	OIII 18.4									
Insula (%)	OII 18.7	15.4					21.1	16.2		
	OIII 9.2									
Parietal (%)	OII 8.2	8.4			26.5		9.1	9.4		
	OIII 12.2									
Sz. Type										
Partial simple sz.	72.0	30.1	21	18.3	57.2		23.7		41.3	21.9
Partial compl. sz.		31.2	24		15.7		6.6		11.5	5.6
(Secondary) generalized	50.0%	64	64	81.7	58.4		69.7		47.1	73.0

A: Astrocytoma; OA: Oligoastrocytoma; OD: Oligodendroglioma; Sz: Seizure.

Table 2. Effect of antitumor therapy on seizure reduction in low-grade gliomas.

	Study (year)	Study	Patients (n)	Subtype	Treatment, follow-up	Seizure reduction (%)
						Seizure freedom
Surgery	Luyken (2003)	Retrospective	15	OD	Surgery, 12 months	87
			35	A	Surgery, 12 months	71
	Chang (2008)	Retrospective	332	LGG	Surgery, 12 months	67
	Englot (2011)	Meta-analysis	773	LGG	Surgery, 6 months	71
	You (2012)	Retrospective	183		Surgery, 12 months	
				29 OD		18
				75 OA		44
			56 A		38	
Radiotherapy	Van den Bent (2005)	Prospective	102	A, OD	Convent RT, 12 months	75
						Reduction of sz. (>50%)
	Ruda (2013)	Retrospective	43	29 A	Convent RT, 3 months	72
				10 OD	Convent RT, 12 months	76
						Seizure freedom
				5 OA		
					Convent RT, 12 months	32
						Reduction of sz. (>50%)
Chemotherapy	Pace (2003)	Retrospective	31	LGG	TMZ, unknown	48
	Hoang-Xuan (2004)	Prospective	60	49 OD	TMZ, unknown	51
				11 OA		
	Kaloshi (2007)	Retrospective	149	105 OD	TMZ, unknown	58
				44 other LGG		
	Lebrun (2007)	Retrospective	33	OD	PCV, unknown	53
	Sherman (2011)	Retrospective	39	LGG	TMZ, median	59
					7 TMZ cycles	
	Koekkoek (2015)	Retrospective	66	LGG	TMZ, 6 months	44
A: Astrocytoma; Convent RT: Conventional radiation therapy; CCNU: Vincristine chemotherapy; LEV: Levetiracetam; LGG: Low-grade glioma; OA: Oligoastrocytoma; OD: Oligodendroglioma; PCV: Procarbazine; TMZ: Temozolomide; Sz: Seizure.						

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as either initial treatment or following surgery and radiotherapy is well established. These agents also improve seizure control [17,24,46]. Administration of temozolomide results in 50% seizure reduction or more in 44–59% of patients with low-grade gliomas, including oligodendrogliomas (Table 2) [24,46–50]. Overall, 20–40% of patients become seizure-free by administration of systemic chemotherapy.

Anticonvulsants: practical management

Choice of anticonvulsants of seizures in brain tumors patients is essentially not different from focal or symptomatic type of epilepsy in adults. Their rationale is based on randomized trials, for this frequently occurring type of partial epilepsy in adults. As such, levetiracetam, zonisamide, carbamazepine and phenytoin show level A evidence of efficacy (defined by trial quality) as initial monotherapy for adults with partial onset seizures. Valproic acid shows level B efficacy, and gabapentin, lamotrigine, oxcarbazepine,

phenobarbital, topiramate and vigabatrin level C [51]. The second factor of choice among these approved AEDs are the individual patient factors like age, sex, weight, comorbidity or cotherapy including the risk on drug–drug interactions [52]. For that reason, in brain tumor patients, one prefers to avoid strong enzyme-inducing AEDs carbamazepine and phenytoin [53,54]. Over the years, this rule has gained in significance in low- and high-grade gliomas by the increasing use of concurrent chemotherapy and the availability of second- and third-generation anticonvulsants with overall good tolerability and relatively few drug interactions [53,54].

Levetiracetam as monotherapy demonstrates high-seizure responses of 70–100% in low- and high-grade gliomas, although antitumor directed therapy probably contributes to these impressive results [55,56]. Add-on treatment (second line polytherapy) with levetiracetam in patients with primary brain tumors produces a 50% reduction in seizures in approximately 65% of

patients [55,56]. Levetiracetam is a well-tolerated anticonvulsant and may even show improvement of cognition, both in general epilepsy as in low-grade gliomas [57,58]. Another advantage of its use is absence of drug interactions [59]. Its most important side effect is irritability leading to withdrawal in 5% of patients [60]. A comparative trial in the early postoperative period has shown better efficacy and tolerability than phenytoin [61].

The effects of valproic acid have been extensively reported in low- and high-grade gliomas showing seizure-freedom or seizure response in 55–78% on monotherapy [20,56,62,63]. Valproic is generally well-tolerated with few cognitive side effects, although it may cause increased appetite, trembling and congenital abnormalities when taken during pregnancy [64]. In oncology, it leads to few drug interactions, although it may aggravate chemotherapy-induced thrombopenia and neutropenia by a direct effect on bone marrow cells [65,66].

In case of insufficient AED monotherapy, there is a trend to apply anticonvulsant polytherapy as the next step [67–69]. Combinations of levetiracetam with AEDs that influence GABA-ergic or glutaminergic activity seem to work synergistically [70]. Indeed, when monotherapy with either levetiracetam or valproic acid is not sufficient, combining the two results in 60% seizure freedom of remaining patients as observed in GBM [56]. A crucial advantage of synergistic therapy is that effective lower doses of AEDs carry smaller risks on toxicity, although this needs confirmation in prospective studies.

On the issue of seizure prophylaxis, comparative trials on the use of AEDs have not shown clear efficacy in tumor-related epilepsy [71].

Pharmacoresistance

Refractory epilepsy in LGG before initial surgery is seen in 50% of patients, and following surgery despite anticonvulsant therapy in 15–40% of cases [18,72,73]. Oligodendrogliomas are more frequently associated with pharmacoresistant epilepsy than with other types of low-grade gliomas. One hypothesis to explain treatment resistance presumes alterations in drug targets affecting antiepileptic drugs binding. Another hypothesis is overexpression of proteins belonging to the ATP-binding cassette transporter family, such as P-gp (MDR1), MRP1 and MRP5, leading to diminished intracellular drug transport [73,74]. In epileptogenic brain tissue, upregulation of these

multidrug resistant proteins may restrain access of anti-epileptic drugs into the brain parenchyma. This overexpression may be intrinsic or acquired during treatment, and may play also role in chemotherapy resistance of glioma cells [75]. Increased intercellular glutamate may contribute to upregulation of multidrug resistant proteins. A number of anti-epileptic drugs, including phenytoin, phenobarbital, carbamazepine and lamotrigine constitute probable substrates for P-gp. Levetiracetam and valproic acid seem to be less affected, and thus less easily associated with refractoriness of seizures to therapy [76]. Valuable options to counter refractory seizures in gliomas are the adjustment of the anticonvulsant regimen by therapeutic drug monitoring, or the administering of antitumor directed therapy including reoperation or epilepsy surgery, and radiation or chemotherapy [77,78].

Drug interactions

The most common drug–drug interactions are of pharmacokinetic nature. This occurs when drugs influence the activity of liver enzymes that they both share for their metabolism [79]. The classical anti-epileptic drugs phenobarbital, carbamazepine and phenytoin are strong inducers of the cytochrome P450 co-enzyme system, particularly of CYPs 2C9, 2C19 and 3A4 co-enzymes. In oncology, many chemotherapeutic agents and tyrosine-kinase inhibitors are metabolized by the 3A4 co-enzyme. The combination of enzyme-inducing anticonvulsants with etoposide and vincristine as part of the PCV chemotherapeutic regimen results in a faster clearance of about a factor 1.5 if dose adjustment is not applied [80,81]. The clearance of cyclophosphamide, irinotecan, paclitaxel and teniposide becomes about two- to threefold faster together with concurrent enzyme inducers, and up to fourfold in combination with the TKIs crizotinib, dasatinib, imatinib and lapatinib [81,82]. The frequently applied chemotherapeutic agents in neuro-oncology temozolomide and bevacizumab are neither prone nor susceptible to drug–drug interaction.

Side effects of CNS bone-marrow & skin

AEDs can influence cognitive functioning. In neuro-oncology, the cumulative effects of previous surgery, radiation therapy, chemotherapy, the presence of epilepsy and the taking of anticonvulsants all contribute to cognitive dysfunction [83–85]. Of these, only the anticonvulsant regimen is amenable to change. Phenobarbital,

phenytoin and carbamazepine are relatively often associated with cognitive side effects showing impairments in memory, mental speed and attention, particularly phenobarbital [86]. The newer AEDs confer less pronounced cognitive dysfunction, with the exception of topiramate [87]. In clinical practice, it can be difficult to distinguish whether cognitive dysfunction is caused by the adverse effects of seizure therapy, by tumor progression, the late effects of previous antitumor treatment or by metabolic, or toxic encephalopathies secondary to organ dysfunction or concurrent drug therapy [85].

Bone marrow suppression and liver dysfunction can occur as a side effect of a number of individual AEDs, and occur more frequently with brain tumors than in general epilepsy [53]. This may be explained by overlapping adverse events with cytotoxic drugs. For example, hematotoxicity secondary to temozolomide or other chemotherapeutic agents can be aggravated by administration of phenobarbital, phenytoin, carbamazepine or valproic acid [88,89]. Thrombopenia may occur as idiosyncratic side-effect of valproic acid, particularly in children and the elderly. In adults, the use of valproic acid as single agent leads much less to clinically significant thrombopenia, and retrospective studies indicate that its combination with temozolomide does not lead to more frequent or severe thrombopenia as compared with levetiracetam or no AEDs [88,90].

Allergic reactions of the skin may occur with a number of AEDs, usually at the time of initiating therapy. This is mainly seen with phenobarbital, phenytoin, carbamazepine, valproic acid, oxcarbazepine and lamotrigine. The most common type of hypersensitivity is a skin rash and its frequency seems higher in patients carrying a brain tumor than in non-tumoral epilepsy [91,92]. More severe and rare allergic reactions are erythema multiforme or Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis which can lead to mortality. Observations suggest that the appearance of SJS in neuro-oncology particularly happens in patients undergoing cranial irradiation and receiving anticonvulsants, particularly phenytoin [92,93]. Recently, the human leukocyte antigen (HLA) class I allele B*1502 has been associated with the appearance of SJS in combination with carbamazepine, phenytoin and oxcarbazepine in Asian populations [94,95]. In other populations including Europe, the HLA-A*3101 allele increases the risk on

carbamazepine-induced hypersensitivity [96]. By screening patients on specific HLA alleles before initiating carbamazepine or phenytoin, these sometimes life-threatening skin reactions can be prevented [96].

Conclusion & future perspective

In recent years, considerable gain in knowledge has been achieved in the field of tumor-related epilepsy. In the large majority of patients with low-grade gliomas, particularly oligodendrogliomas, seizures constitute the first clinical sign necessitating diagnostic work up and subsequent treatment. Often, epilepsy is the presenting and only clinical symptom of a low-grade glioma, representing an independent prognostic factor for long-term survival, strongly associated with the presence of the IDH1 mutation. Recurrence of seizures following a relatively long period of seizure-freedom may represent tumor progression. Surgery, radiotherapy and chemotherapy contribute all to seizure control. Symptomatic management with levetiracetam or valproic acid are the preferred monotherapy choices among the evidence-based anticonvulsants for symptomatic epilepsies. They are effective in two-thirds or more of patients with tumor-related epilepsy. Combining both in case of insufficient seizure control on monotherapy leads to a good efficacy in 60% of the remaining patients. Indications that levetiracetam works synergistically with other anticonvulsants including valproic acid also warrants further study. Pharmacoresistant seizures are not rare occurring in about 40% of oligodendrogliomas. Adapting the anticonvulsant regimen based on therapeutic drug monitoring or applying antitumor directed therapy can be effective in case of pharmacoresistant epilepsy. Toxicity of the nervous system is a potential side effect of all anticonvulsants, and seems more prevalent in tumoral epilepsy by the effects of earlier antitumor directed therapies or by the use of concurrent drugs.

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References

- 1 Lee JW, Wen PY, Hurwitz S *et al.* Morphological characteristics of brain tumors causing seizures. *Arch. Neurol.* 67(3), 336–342 (2010).
- 2 de Groot M, Reijneveld JC, Aronica E, Heimans JJ. Epilepsy in patients with a brain tumour: focal epilepsy requires focused treatment. *Brain* 135, 1002–1016 (2012).
- 3 van Breemen MSM, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurol.* 6(5), 421–430 (2007).
- 4 van Dellen E, Douw L, Hillebrand A *et al.* MEG network differences between low- and high-grade glioma related to epilepsy and cognition. *PLoS ONE* 7(11), e50122 (2012).
- 5 de Groot M, Toering ST, Boer K *et al.* Expression of synaptic vesicle protein 2A in epilepsy-associated brain tumors and in the peritumoral cortex. *Neuro Oncol.* 12(3), 265–273 (2010).
- 6 Prabowo AS, Iyer AM, Veersema TJ *et al.* BRAF V600E mutation is associated with mTOR signaling activation in glioneuronal tumors. *Brain Pathol.* 24(1), 52–66 (2014).
- 7 Houillier C, Wang X, Kaloshi G *et al.* IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. *Neurology* 75(17), 1560–1566 (2010).
- 8 Liubinas SV, D'Abaco GM, Moffat BM *et al.* IDH1 mutation is associated with seizures and protoplasmic subtype in patients with low-grade gliomas. *Epilepsia* 55(9), 1438–1443 (2014).
- 9 Zhong Z, Wang Z, Wang Y, You G, Jiang T. IDH1/2 mutation is associated with seizure as an initial symptom in low-grade glioma: a report of 311 Chinese adult glioma patients. *Epilepsy Res.* 109, 100–105 (2015).
- 10 Liang R, Fan Y, Wang X, Mao Q, Liu Y. The significance of IDH1 mutations in tumor-associated seizure in 60 Chinese patients with low-grade gliomas. *Scientific World J.* 2013, 403942–403942 (2013).
- 11 Pallud J, Audureau E, Blonski M *et al.* Epileptic seizures in diffuse low-grade gliomas in adults. *Brain* 137, 449–462 (2014).
- 12 Rosati A, Poliani PL, Todeschini A *et al.* Glutamine synthetase expression as a valuable marker of epilepsy and longer survival in newly diagnosed glioblastoma multiforme. *Neuro Oncol.* 15(5), 618–625 (2013).
- 13 Pallud J, Van Quyen ML, Bielle F *et al.* Cortical GABAergic excitation contributes to epileptic activities around human glioma. *Sci. Transl. Med.* 6(244) (2014).
- 14 Omuro AMP, Faivre S, Raymond E. Lessons learned in the development of targeted therapy for malignant gliomas. *Mol. Cancer Ther.* 6(7), 1909–1919 (2007).
- 15 Boer K, Troost D, Timmermans W *et al.* Cellular localization of metabotropic glutamate receptors in cortical tubers and subependymal giant cell tumors of tuberous sclerosis complex. *Neuroscience* 156(1), 203–215 (2008).
- 16 Curatolo P, Moavero R. mTOR inhibitors in tuberous sclerosis complex. *Curr. Neuropharmacol.* 10(4), 404–415 (2012).
- 17 Ruda R, Bello L, Duffau H, Soffietti R. Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. *Neuro Oncol.* 14, 55–64 (2012).
- 18 Smits A, Duffau H. Seizures and the Natural History of World Health Organization Grade II Gliomas: a review. *Neurosurgery* 68(5), 1326–1333 (2011).
- 19 Nataf F, Koziak M, Ricci AC *et al.* Results of the Sainte-Anne-Lyons series of 318 oligodendroglioma in adults. *Neurochirurgie* 51(3–4), 329–351 (2005).
- 20 van Breemen MSM, Rijsman RM, Taphoorn MJB, Walchenbach R, Zwinkels H, Vecht CJ. Efficacy of anti-epileptic drugs in patients with gliomas and seizures. *J. Neurol.* 256(9), 1519–1526 (2009).
- 21 Mirsattari SM, Chong JJR, Hammond RR *et al.* Do epileptic seizures predict outcome in patients with oligodendroglioma? *Epilepsy Res.* 94(1–2), 39–44 (2011).
- 22 Huang L, You G, Jiang T, Li G, Li S, Wang Z. Correlation between tumor-related seizures and molecular genetic profile in 103 Chinese patients with low-grade gliomas: a preliminary study. *J. Neurol. Sci.* 302(1–2), 63–67 (2011).
- 23 Chang EF, Potts MB, Keles GE *et al.* Seizure characteristics and control following resection in 332 patients with low-grade gliomas. *J. Neurosurg.* 108(2), 227–235 (2008).
- 24 Koekkoek JAF, Dirven L, Heimans JJ *et al.* Seizure reduction in a low-grade glioma: more than a beneficial side effect of temozolomide. *J. Neurol. Neurosurg. Psychiatry* 86(4), 366–373 (2015).
- 25 Yuen TI, Morokoff AP, Bjorksten A *et al.* Glutamate is associated with a higher risk of seizures in patients with gliomas. *Neurology* 79(9), 883–889 (2012).
- 26 Englot DJ, Berger MS, Barbaro NM, Chang EF. Factors associated with seizure freedom in the surgical resection of glioneuronal tumors. *Epilepsia* 53, (1), 51–57 (2012).
- 27 Pignatti F, van den Bent M, Curran D *et al.* Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J. Clin. Oncol.* 20(8), 2076–2084 (2002).
- 28 Leighton C, Fisher B, Bauman G *et al.* Supratentorial low-grade glioma in adults: an analysis of prognostic factors and timing of radiation. *J. Clin. Oncol.* 15(4), 1294–1301 (1997).
- 29 van Veelen ML, Avezaat CJ, Kros JM, van Putten W, Vecht C. Supratentorial low grade astrocytoma: prognostic factors, dedifferentiation, and the issue of early versus late surgery. *J. Neurol. Neurosurg. Psychiatry* 64(5), 581–587 (1998).
- 30 Stockhammer F, Misch M, Helms H-J *et al.* IDH1/2 mutations in WHO grade II astrocytomas associated with localization and seizure as the initial symptom. *Seizure* 21(3), 194–197 (2012).
- 31 Scheie D, Meling TR, Cvancarova M *et al.* Prognostic variables in oligodendroglial tumors: a single-institution study of 95 cases. *Neuro Oncol.* 13(11), 1225–1233 (2011).
- 32 Sahm F, Reuss D, Koelsche C *et al.* Farewell to oligoastrocytoma: *in situ* molecular genetics favor classification as either oligodendroglioma or astrocytoma. *Acta Neuropathol.* 128(4), 551–559 (2014).
- 33 Sanson M, Marie Y, Paris S *et al.* Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. *J. Clin. Oncol.* 27(25), 4150–4154 (2009).
- 34 Kerkhof M, Vecht CJ. Seizure characteristics and prognostic factors of gliomas. *Epilepsia* 54(Suppl. 9), 12–17 (2013).
- 35 Luyken C, Blumcke I, Fimmers R *et al.* The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. *Epilepsia* 44(6), 822–830 (2003).
- 36 Chang EF, Potts MB, Keles GE *et al.* Seizure characteristics and control following resection in 332 patients with low-grade gliomas. *J. Neurosurg.* 108(2), 227–235 (2008).
- 37 Englot DJ, Berger MS, Barbaro NM, Chang EF. Predictors of seizure freedom after resection of supratentorial low-grade gliomas. A review. *J. Neurosurg.* 115(2), 240–244 (2011).
- 38 Luyken C, Blumcke I, Fimmers R *et al.* The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. *Epilepsia* 44(6), 822–830 (2003).

- 39 Zaatreh MM, Firlik KS, Spencer DD, Spencer SS. Temporal lobe tumoral epilepsy: characteristics and predictors of surgical outcome. *Neurology* 61(5), 636–641 (2003).
- 40 Benifla M, Otsubo H, Ochi A *et al.* Temporal lobe surgery for intractable epilepsy in children: an analysis of outcomes in 126 children. *Neurosurgery* 59(6), 1203–1213; discussion 1213–1204 (2006).
- 41 Warnke PC, Berlis A, Weyerbrock A, Ostertag CB. Significant reduction of seizure incidence and increase of benzodiazepine receptor density after interstitial radiosurgery in low-grade gliomas. *Acta Neurochir.* 68(Suppl.) 90–92 (1997).
- 42 Shankar A, Rajshekhar V. Radiological and clinical outcome following stereotactic biopsy and radiotherapy for low-grade insular astrocytomas. *Neurol. India* 51(4), 503–506 (2003).
- 43 Ruda R, Magliola U, Bertero L *et al.* Seizure control following radiotherapy in patients with diffuse gliomas: a retrospective study. *Neuro Oncol.* 15(12), 1739–1749 (2013).
- 44 Scerrati M, Montemaggi P, Iacoangeli M, Roselli R, Rossi GF. Interstitial brachytherapy for low-grade cerebral gliomas – analysis of results in a series of 36 cases. *Acta Neurochir.* 131(1–2), 97–105 (1994).
- 45 van den Bent MJ, Afra D, de Witte O *et al.* Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet* 366(9490), 985–990 (2005).
- 46 Pace A, Vidiri A, Galie E *et al.* Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. *Ann. Oncol.* 14(12), 1722–1726 (2003).
- 47 Hoang-Xuan K, Capelle L, Kujas M *et al.* Temozolomide as initial treatment for adults with low-grade oligodendrogliomas or oligoastrocytomas and correlation with chromosome 1p deletions. *J. Clin. Oncol.* 22(15), 3133–3138 (2004).
- 48 Kaloshi G, Benouaich-Amiel A, Diakite F *et al.* Temozolomide for low-grade gliomas – predictive impact of 1p/19q loss on response and outcome. *Neurology* 68(21), 1831–1836 (2007).
- 49 Lebrun C, Fontaine D, Bourg V *et al.* Treatment of newly diagnosed symptomatic pure low-grade oligodendrogliomas with PCV chemotherapy. *Eur. J. Neurol.* 14(4), 391–398 (2007).
- 50 Sherman JH, Moldovan K, Yeoh HK *et al.* Impact of temozolomide chemotherapy on seizure frequency in patients with low-grade gliomas. *J. Neurosurg.* 114(6), 1617–1621 (2011).
- 51 Glauser T, Ben-Menachem E, Bourgeois B *et al.* Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 54(3), 551–563 (2013).
- 52 Karceski S, Morrell MJ, Carpenter D. Treatment of epilepsy in adults: expert opinion, 2005. *Epilepsy Behav.* 7, S1–S64 (2005).
- 53 Glantz MJ, Forsyth PA, Recht LD *et al.* Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors – report of the quality standards subcommittee of the american academy of neurology. *Neurology* 54(10), 1886–1893 (2000).
- 54 Soffietti R, Baumert BG, Bello L *et al.* Guidelines on management of low-grade gliomas: report of an EFNS-EANO* task force. *Eur. J. Neurol.* 17(9), 1124–1133 (2010).
- 55 Maschio M, Dinapoli L, Sperati F *et al.* Levetiracetam monotherapy in patients with brain tumor-related epilepsy: seizure control, safety, and quality of life. *J. Neurooncol.* 104(1), 205–214 (2011).
- 56 Kerkhof M, Dielemans JCM, van Breemen MS *et al.* Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme. *Neuro Oncol.* 15(7), 961–967 (2013).
- 57 Witt JA, Helmstaedter C. The effects of levetiracetam on cognition – a noninterventional surveillance study. *Epilepsia* 50, 227–227 (2009).
- 58 de Groot M, Douw L, Sizoo EM *et al.* Levetiracetam improves verbal memory in high-grade glioma patients. *Neuro Oncol.* 15(2), 216–223 (2013).
- 59 Vecht CJ, Wagner GL, Wilms EB. Treating seizures in patients with brain tumors: Drug interactions between antiepileptic and chemotherapeutic agents. *Semin. Oncol.* 30(6 Suppl. 19), 49–52 (2003).
- 60 Mbizvo GK, Dixon P, Hutton JL, Marson AG. Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. *Cochrane Database Syst. Rev.* (9) (2012).
- 61 Lim DA, Tarapore P, Chang E *et al.* Safety and feasibility of switching from phenytoin to levetiracetam monotherapy for glioma-related seizure control following craniotomy: a randomized Phase II pilot study. *J. Neurooncol.* 93(3), 349–354 (2009).
- 62 Wick W, Menn O, Meisner C *et al.* Pharmacotherapy of epileptic seizures in glioma patients: who, when, why and how long? *Onkologie* 28(8–9), 391–396 (2005).
- 63 You G, Huang L, Yang P *et al.* Clinical and molecular genetic factors affecting postoperative seizure control of 183 Chinese adult patients with low-grade gliomas. *Eur. J. Neurol.* 19(2), 298–306 (2012).
- 64 Bodalia PN, Grosso AM, Sofat R *et al.* Comparative efficacy and tolerability of anti-epileptic drugs for refractory focal epilepsy: systematic review and network meta-analysis reveals the need for long term comparator trials. *Br. J. Clin. Pharmacol.* 76(5), 649–667 (2013).
- 65 Bourg V, Lebrun C, Chichmanian RM, Thomas P, Frenay M. Nitroso-urea-cisplatin-based chemotherapy associated with valproate: Increase of haematologic toxicity. *Ann. Oncol.* 12(2), 217–219 (2001).
- 66 Weller M, Gorlia T, Cairncross JG *et al.* Prolonged survival with valproic acid use in the EORTC/NCIC temozolomide trial for glioblastoma. *Neurology* 77(12), 1156–1164 (2011).
- 67 French JA, Faught E. Rational polytherapy. *Epilepsia* 50, 63–68 (2009).
- 68 Stephen LJ, Brodie MJ. Antiepileptic drug monotherapy versus polytherapy: pursuing seizure freedom and tolerability in adults. *Curr. Opin. Neurol.* 25(2), 164–172 (2012).
- 69 Brodie MJ, Sills GJ. Combining antiepileptic drugs – rational polytherapy? *Seizure* 20(5), 369–375 (2011).
- 70 Kaminski RM, Matagne A, Patsalos PN, Klitgaard H. Benefit of combination therapy in epilepsy: a review of the preclinical evidence with levetiracetam. *Epilepsia* 50(3), 387–397 (2009).
- 71 Sayegh ET, Fakurnejad S, Oh T, Bloch O, Parsa AT. Anticonvulsant prophylaxis for brain tumor surgery: determining the current best available evidence. *J. Neurosurg.* 121(5), 1139–1147 (2014).
- 72 You G, Sha Z-Y, Yan W *et al.* Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study. *Neuro Oncol.* 14(2), 230–241 (2012).
- 73 Calatuzzolo C, Pollo B, Botturi A *et al.* Multidrug resistance proteins expression in glioma patients with epilepsy. *J. Neurooncol.* 110(1), 129–135 (2012).
- 74 Alms D, Fedorowicz M, Roermann K, Noack A, Loeschner W. Marked differences in the effect of antiepileptic and cytostatic drugs on the functionality of p-glycoprotein in human and rat brain capillary endothelial cell lines. *Pharm. Res.* 31(6), 1588–1604 (2014).
- 75 Stepien KM, Tomaszewski M, Tomaszewska J, Czuczwar SJ. The multidrug transporter

- P-glycoprotein in pharmacoresistance to antiepileptic drugs. *Pharmacol. Rep.* 64(5), 1011–1019 (2012).
- 76 Zhang C, Kwan P, Zuo Z, Baum L. The transport of antiepileptic drugs by P-glycoprotein. *Adv. Drug Deliv. Rev.* 64(10), 930–942 (2012).
- 77 Vecht CJ, Kerkhof M, Duran-Pena A. Seizure prognosis in brain tumors: new insights and evidence-based management. *Oncologist* 19(7), 751–759 (2014).
- 78 Koekoek JAF, Kerkhof M, Dirven L, Heimans JJ, Reijneveld JC, Taphoorn MJB. Seizure outcome after radiotherapy and chemotherapy in low-grade glioma patients: a systematic review. *Neuro Oncol.* 17(7), 924–934 (2015).
- 79 Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia* 54(1), 11–27 (2013).
- 80 Benit CP, Vecht CJ. Spectrum of side-effects of anticonvulsants in patients with brain tumours. *Eur. Assoc. Neuro Oncol. Mag.* 2(1), 15–24 (2012).
- 81 Yap KY, Chui WK, Chan A. Drug interactions between chemotherapeutic regimens and antiepileptics. *Clin. Ther.* 30(8), 1385–1407 (2008).
- 82 Vecht CJ, Wagner GL, Wilms EB. Interactions between antiepileptic and chemotherapeutic drugs. *Lancet Neurol.* 2(7), 404–409 (2003).
- 83 Klein M, Engelberts NHJ, van der Ploeg HM *et al.* Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. *Ann. Neurol.* 54(4), 514–520 (2003).
- 84 Taphoorn MJ. Neurocognitive sequelae in the treatment of low-grade gliomas. *Semin. Oncol.* 30(6 Suppl 19), 45–48 (2003).
- 85 Ricard D, De Greslan T, Soussain C *et al.* Neurological damage of brain tumor therapy. *Rev. Neurol.* 164(6–7), 575–587 (2008).
- 86 Brunbech L, Sabers A. Effect of antiepileptic drugs on cognitive function in individuals with epilepsy – a comparative review of newer versus older agents. *Drugs* 62(4), 593–604 (2002).
- 87 Mula M, Trimble MR. Antiepileptic drug-induced cognitive adverse effects potential mechanisms and contributing factors. *CNS Drugs* 23(2), 121–137 (2009).
- 88 Simo M, Velasco R, Graus F *et al.* Impact of antiepileptic drugs on thrombocytopenia in glioblastoma patients treated with standard chemoradiotherapy. *J. Neurooncol.* 108(3), 451–458 (2012).
- 89 Hildebrand J, Lecaillon C, Perennes J, Delattre JY. Epileptic seizures during follow-up of patients treated for primary brain tumors. *Neurology* 65(2), 212–215 (2005).
- 90 Tinchon A, Oberndorfer S, Marosi C *et al.* Haematological toxicity of valproic acid compared with Levetiracetam in patients with glioblastoma multiforme undergoing concomitant radio-chemotherapy: a retrospective cohort study. *J. Neurol.* 262(1), 179–186 (2015).
- 91 Mamon HJ, Wen PY, Burns AC, Loeffler JS. Allergic skin reactions to anticonvulsant medications in patients receiving cranial radiation therapy. *Epilepsia* 40(3), 341–344 (1999).
- 92 Bishop AJ, Chang M, Lacouture ME, Barker CA. EMPACT syndrome: limited evidence despite a high-risk cohort. *J. Neurooncol.* 119(1), 129–134 (2014).
- 93 Delattre JY, Safai B, Posner JB. Erythema multiforme and Stevens-Johnson syndrome in patients receiving cranial irradiation and phenytoin. *Neurology* 38(2), 194–198 (1988).
- 94 Wu T, Chen C-C, Chen T-C *et al.* Clinical efficacy and cognitive and neuropsychological effects of levetiracetam in epilepsy: an open-label multicenter study. *Epilepsy Behav.* 16(3), 468–474 (2009).
- 95 Chen P, Lin J-J, Lu C-S *et al.* Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *N. Engl. J. Med.* 364(12), 1126–1133 (2011).
- 96 McCormack M, Alfrevic A, Bourgeois S *et al.* HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N. Engl. J. Med.* 364(12), 1134–1143 (2011).