Editorial

Glioma-associated epilepsy: toward mechanism-based treatment

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Abstract: Epilepsy is common in glioma patients, and glioma-related epilepsy has a strong impact on patients' quality of life. Glioma-related epilepsy has a unfavorable clinical course when compared to other types of symptomatic epilepsy, with low rates of seizure freedom, common relapses of seizures after seizure-free periods, and a severe outcome in case of intractable seizures (status epilepticus). Translational research is starting to elucidate the specific pathophysiological mechanisms in this disease: the molecular-biological characteristics of the tumor result in metabolic changes in the glioma and the peritumoral region. These changes lead to abnormal neuronal and non-neuronal signaling changes in the tumor's surroundings and in the brain's global functional network ("connectome"). Anti-neoplastic treatments often cause amelioration of epilepsy, possibly by reverting the pathophysiological pro-epileptogenic processes in the tumor. Further research should focus on these pathophysiological mechanisms and on the possibilities for new mechanism-based anti-epileptic treatments. Clinical trials for gliomas should incorporated epilepsy as an outcome measure.

Keywords: Epilepsy; glioma; glioblastoma; pathophysiology

Introduction

Patients with a diffuse glioma suffer from both a progressive and incurable neoplasm, as well as from a brain disease. Epilepsy is one of the most common symptoms in these patients, with substantial impact on quality of life. Glioma-associated epilepsy is mostly viewed as a common and generic manifestation of brain disease (regardless of the exact type of brain pathology). Consequently, treatment protocols for epilepsy mostly lack specific guidelines for glioma patients. However, empirical data suggest that glioma-associated epilepsy differs from other types of epilepsy regarding underlying mechanism, clinical manifestation and response to treatments. A recent study by Neal *et al.* in *Epilepsia* provides important insights from clinical practice on this matter (1). On the basis of such clinical findings, as well as recent translational work, we argue that glioma-associated epilepsy should be studied as a separate entity, with input from neuroscience and oncobiology; with specific mechanism-based treatments as a result.

The diffuse gliomas

Adult diffuse gliomas [World Health Organization (WHO) grade 2 to 4] are progressive neoplasms of brain or spinal cord which are characterized by a pattern of infiltrative growth into healthy brain tissue and a high degree of resistance to available antineoplastic treatments. Until recently, diffuse gliomas were classified according to (I) cell type of presumed origin (astrocytoma, oligodendroglioglioma, or a mixed type) and (II) WHO grade, which reflects histopathological signs of aggressiveness, and is correlated with prognosis. In the 2016 revision of the WHO's criteria for tumors of the central nervous

system, diffuse gliomas are classified according to a system of "layered diagnosis". Histopathological findings are combined with molecular-genetic data, with a distinct role of certain genetic and epigenetic markers.

Life expectancy in diffuse gliomas is highly variable, but shortened. Survival of young patients with a low-grade (WHO grade 2) oligodendroglioma and a favorable molecular profile far exceeds 12 years (2). In contrast, patients with a typical glioblastoma (WHO grade 4, IDH-wild type, 50 or older) mostly do not survive beyond two years following initial diagnosis (3).

Symptoms of glioma patients differ from the general cancer population in many aspects. Most notably, patients —specifically those with lower-grade gliomas—may remain physically fit for a long time, but will mostly suffer from increasing symptoms of cerebral dysfunction. Cerebral symptoms include cognitive deficits, fatigue, behavioral changes, focal neurological deficits such as paresis or aphasia, and epilepsy.

Glioma-associated epilepsy

The hallmark feature of any type of epilepsy are seizures: abnormal electrical discharges in the brain's neocortex, either in a focal brain region or generalized throughout the brain. The exact clinical manifestation of seizures is determined by the location in the brain where the seizure arises ("epileptogenic zone"). Epilepsy may be idiopathic (genetic) or may be symptomatic: a manifestation of an underlying brain disease. Patients' quality of life is compromised because of the direct discomfort of seizures, the post-ictal symptoms (e.g., temporary neurological deficits or fatigue), the side effects of medication, and the legal and psychological consequences of having seizures (anxiety, inability to drive a car). Consequently, quality of life is worst in patients with uncontrolled seizures, and complete seizure-freedom is the strongest predictor of good quality of life (4).

Glioma-associated epilepsy is a type of symptomatic focal epilepsy, which may manifest with focal seizures, generalized seizures, or both. Epilepsy occurs in >80% of patients with a low-grade glioma and 40–60% of patients with glioblastoma (5,6). It is often the first clear presentation of the glioma.

Rather than being "just another type of epilepsy", glioma-associated epilepsy is characterized by a specific clinical profile, which we will summarize below. We will then describe findings from preclinical and translational research that are providing an initial insight into the unique

underlying mechanisms: a complex interplay between the tumor, the peritumoral microenvironment and the brain as a whole.

Clinical profile

An increasing number of observations from clinical practice point towards a distinct clinical course in glioma-associated epilepsy. Firstly, in contrast to many other causes of epilepsy (e.g., post-stroke-epilepsy), diffuse gliomas are progressive in nature; consequently, the severity of epilepsy and type of seizures may also evolve in parallel with the underlying tumor. A spontaneous worsening of epilepsy (recurrence after prolonged seizure-freedom, or an increased frequency of seizures) is a clinical predictor of progression of the glioma (7). Secondly, a substantial proportion of patients with tumor-associated epilepsy do not obtain seizure freedom despite the use of multiple anti-epileptic drugs. Studies suggest that ~20% or more of patients across all types of epilepsy do not become seizure-free (8); in glioma-associated epilepsy, reported rates of drug-resistant epilepsy are worse, varying between 23% and 87% depending on subpopulation and study type (9-11). Thirdly, status epilepticus has a more severe course in glioma patients than in patients with epilepsy other due to other causes. Status epilepticus is a debilitating and potentially life-threatening medical emergency, defined by a continuous seizure for 30 minutes or more. In a meta-analysis, status epilepticus due to brain tumors (including gliomas) was associated with higher mortality and possibly longer duration than status epilepticus due to other causes (12). A focused retrospective cohort study showed that status epilepticus in glioma and other tumors, when compared to other causes of status epilepticus, is associated with longer duration of seizures, more and longer postictal (temporary) neurological deficits and a higher rate of long-term neurological deficits, even when the underlying tumor is stable (13).

A noteworthy addition to the clinical data on glioma-associated epilepsy comes from a retrospective cohort study, recently published in *Epilepsia*, on seizure patterns and post-operative seizure control in diffuse glioma. Neal *et al.* retrospectively studied postoperative seizure control in a group of 186 patients with diffuse gliomas. A total of 64% of patients suffered from glioma-associated epilepsy, either pre-operatively, post-operatively, or both. The authors classified the postoperative seizure outcome as (I) no postoperative seizures, in 51%; (II) early postoperative seizure control, with seizures within but not beyond six

months postoperatively, in 12%; (III) fluctuating seizure control, with ongoing seizures interspersed with seizure-free periods of at least six months, in 24%; and (IV) ongoing seizures in 13%. Patients with a glioblastoma (grade 4) had a better chance of good seizure outcome (pattern a or b) than patients with grade 2–3 glioma. Risk factors for ongoing seizures were the presence of one or more pre-operative seizures and having a partial or subtotal resection rather than a gross total resection of the tumor mass. A noteworthy finding was the fact that, of all patients who experienced a long (>12 months) period of seizure-freedom, 38% subsequently suffered one or more seizures again. The latter finding probably reflects the dynamic and progressive course of the underlying gliomas. Concerning the effect of anti-epileptic medication, the first regimen resulted in 12-month seizure freedom in 23% of patients, the second regimen in another 7% and further regimens in only 5% more; these numbers are poor when compared to the general epilepsy population.

Several limitations inherent to a retrospective study are apparent. Most particularly, seizure outcome is dependent on the management of epilepsy and the choice of anti-epileptic drugs. These policies were determined by the treating physician—without a strict protocol—and the timeframe of the study (1988–2011), and commonly included older anti-epileptic drugs such as phenytoin. Another specific issue concerns the routine use of prophylactic peri-operative anti-epileptic drugs for several months (99% of patients without pre-operative seizures), which is not supported by available guidelines, although many practitioners do use them.

Despite these shortcomings, this cohort study offers large-scale confirmation of earlier findings on the high prevalence of epilepsy in glioma patients, the relatively poor effects of anti-epileptic drugs, and the fluctuating nature of the disease. In addition, the study demonstrates that seizure-freedom is less common in patients with grade 2–3 glioma than in glioblastoma.

Translational research: tumor-dependent mechanisms

The unique clinical profile of glioma-related epilepsy may have several sources. Patient factors that contribute to the severe course of epilepsy may include the use of medication such as chemotherapy and dexamethasone, poor physical functioning, or genetic factors. In addition, accumulating evidence points towards a role of the glioma and its microenvironment causing a pro-epileptogenic environment in the brain.

In a high-quality review of 2012, de Groot et al. summarized available evidence. Pro-epileptogenic changes in the glioma brain occur at several—related—levels: through specific intra-tumoral molecular-biological pathways, through changes in the direct peritumoral region (microenvironment) and between-cell signaling, and through disturbances in the organization of whole-brain signaling as a network (often referred to as the "connectome") (14). A study by Douw et al. offers an elegant demonstration of the relationship between these different levels. In a cohort of patients with gliomas and epilepsy, brain network functioning (connectivity) was quantified with magneto-encephalography, and tumor tissue was studied for expression of proteins with a known role in (glioma-associated) epilepsy. Expression of the proteins synaptic vesicle protein 2A (SV2A) and poly-glycoprotein (P-gp) was associated with degrees of connectivity as well as frequency of seizures. In fact, protein expression of individual tumors could be predicted reliably on the basis of MEG connectivity patterns (15). This study illustrates that molecular-biological alterations in gliomas may facilitate the occurrence of seizures through disturbances in the organization of the brain's functional network, possibly through micro-environmental biochemical changes in the peritumoral region that influence synaptic and non-synaptic cell signaling and excitability.

Another example of the relationship between oncobiological characteristics of gliomas and epilepsy concerns mutations in isocitrate dehydrogenase (IDH), which are common in WHO grade 2 and 3 gliomas, and are more or less unique to diffuse gliomas. In WHO grade 2–3 gliomas, pre-operative seizures occurred more often in IDH-mutated gliomas than in IDH-wild-type gliomas(16). This link is may be due to the fact that IDH mutations result in higher concentrations of the metabolite 2-hydroxyglutarate (2HG) in glioma cells; because of its structural similarity to the neurotransmitter glutamate, 2HG can activate N-methyl-D-aspartate(NMDA)-receptors, causing increased neuronal excitability and increased susceptibility to seizures.

Another illustration of the unique pathophysiology of glioma-related epilepsy comes from a study on glioblastomas (WHO grade 4). Glioblastoma patients who present with epilepsy have a better prognosis than patients without epilepsy at presentation. This association is independent of established prognostic factors (6). As

a possible explanation, glioblastomas with epilepsy at presentation differ in the expression of several oncogenic pathways (Berendsen *et al.*, personal communication). This existence of a specific molecular-biological profile of epileptogenic gliomas supports the view that glioma-related epilepsy has a specific, tumor-related pathophysiology. The specific molecular-biological profile also offers an explanation for the variability in the occurrence and severity of epilepsy among glioma patients; the variability in epilepsy follows directly from the molecular-biological heterogeneity of gliomas.

The insights on the pathophysiological background of glioma-related epilepsy are helpful in understanding the relationship between tumor treatment and the course of epilepsy. All established anti-neoplastic treatment modalities for gliomas are associated with an amelioration of epilepsy. Resective glioma surgery is associated with a decrease of seizure frequency and a chance of seizure-freedom (9,17); pre- or intra-operative localization and resection of the epileptogenic brain region may increase this anti-epileptic effect, but even a "simple" lesionectomy may be helpful. Radiotherapy for low-grade glioma resulted in a decrease of seizures in a randomized trial (18). More recently, similar effects were observed in observational studies on temozolomide in glioma patients (19). Reduction in seizure frequency occurred, even in the context of a stable (i.e., non-shrinking) tumor. The latter finding may, speculatively, mean that successful anti-tumor-treatment causes a reduction – rather than a mere stabilization – of seizures through decreased release of pro-epileptogenic factors in and around the tumor, rather than through a mechanical effect (decreased mass). Alternatively, antineoplastic treatments may directly influence the epileptogenic brain tissue, as has been illustrated for radiotherapy: stereotactic radiosurgery of epileptogenic brain tissue in patients with non-glioma-based epilepsy causes biochemical changes in local neurotransmitter and amino-acid levels (20), possibly resulting in lower neuronal excitability and reduction of seizures.

Toward clinical benefit

To improve quality of life in glioma patients, better control of epilepsy is needed, preferably seizure freedom. The importance of seizure outcome as a response criterion in glioma treatment was recently underlined by a recent review from the international Response Assessment in Neuro-Oncology (RANO) group (21). In this paper, we have argued that glioma-related epilepsy has a unique and

severe clinical phenotype, with a variable but generally poor response to anti-epileptic drugs, but with a beneficial effect of successful anti-tumor treatment. This clinical profile has a specific pathophysiological basis that seems to be rooted in molecular-biological intratumoral changes, microenvironmental disturbances around the tumor, and dysfunction of local and whole-brain network functioning of the brain.

In order to improve seizure outcome in glioma patients, we propose that the following lines of investigation be pursued:

(I)   Specific pathophysiological studies on glioma-related epilepsy with relevant models: pre-clinical in vivo models as well as human studies that integrate molecular-biological typing of gliomas, imaging studies of structural and functional (network) changes in the brain, and thorough clinical evaluation with standardized response metrics;

(II) Studies on existing and new anti-epileptic drugs, or non-pharmacological interventions, should be performed separately in glioma patients. This is specifically true for studies on treatment of status epilepticus. Specific drugs for glioma-related epilepsy may be developed on the basis of recent and future insights on specific molecular-biological pathways;

(III) Clinical trials on antineoplastic treatment in diffuse gliomas should include standardized response metrics on epilepsy.

These lines of research should eventually result in specific treatment protocols for glioma-associated epilepsy, and—ideally—new and specific anti-epileptic drugs. In the meantime, awareness of the severity and specific aspects of glioma-related epilepsy may already contribute to the patients' well-being.

Footnote

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