Editorial

Postoperative seizure control in glioma patients with epilepsy

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Gliomas account for approximately 80% of all primary malignant brain tumors with a rate of 2–8 cases per 100,000 person-years. Gliomas result in a disproportionate share of cancer morbidity, including focal neurological deficits, cognitive impairment and seizures. Seizures may occur in every type of glioma, although the epileptogenicity of gliomas tends to be inversely correlated to the growth rate of the tumor (1). Approximately 70–90% of all patients with low-grade glioma (LGG) develop epilepsy during the course of the disease, in comparison to 30–60% of patients with high-grade glioma (HGG) (2). Gliomas located in the frontal or temporal lobe, as well as cortical located tumors tend to be more epileptogenic (1). In the clinical management of gliomas it is of major importance to achieve seizure control, as seizures may negatively influence health-related quality of life and cause cognitive disturbances, particularly when uncontrolled (3). In spite of using multiple antiepileptic drugs (AEDs), about one third of low-grade glioma patients will not become seizure free (4). In addition, seizure control appears to be a dynamic phenomenon in patients with glioma, fluctuating during the course of the disease. Neal *et al*. aimed to characterize the patterns of postoperative seizure control in glioma patients and identify specific risk factor profiles (5).

In a retrospective single centre review of 186 patients with supratentorial grade II–IV glioma Neal *et al*. distinguished four patterns of postoperative seizure control: (I) completely seizure free; (II) seizures occurring only in the first 6 months postoperatively; (III) seizures alternating by periods of seizure control from 0–24 months postoperatively for at least 6 months, and from 24 months postoperatively for at least 12 months; (IV) never seizure free. In total, 119 patients (64%) were diagnosed with tumor-associated epilepsy, of whom 38 patients developed epilepsy after surgery. In patients with LGG and anaplastic glioma, fluctuating seizure control according to pattern C was most commonly found. Moreover, about two third of these patients showed at least one 12-month period of seizure freedom. The presence of preoperative seizures as well as an incomplete surgical resection were the most important clinical variables associated with seizure pattern D, i.e., patients who never became seizure free (5).

In line with the current literature on epilepsy in glioma patients, Neal *et al*. demonstrate that apart from AED treatment, a surgical resection may at least temporarily contribute to seizure control. Seizure freedom after surgery has previously been reported in 53–87% of LGG patients (6,7). In slow-growing glioneuronal tumors, such as gangliogliomas and dysembryoplastic neuroepithelial tumors (DNTs), long-term seizure freedom was observed in up to 94% of cases (8). In HGG patients with preoperative seizures, 77% of patients became seizure free 1 year after surgery (9). As a gross total resection is one of the strongest predictors of postoperative seizure-freedom, surgery is aimed at performing a maximally safe resection. However, gross total resection is only feasible in approximately half of cases and the epileptogenic zone may be located in extratumoral cortical areas as well (8). As a consequence,

some patients will never become seizure free and refractory seizures may persist in 15–20% of patients after surgery (10,11). In addition, a less favorable outcome after surgery has been observed in case of preoperative seizures or focal seizures despite anti-epileptic drug therapy (6,12).

Although the evidence from the literature is limited, a decrease in seizure frequency has also been found after treatment with radiotherapy or chemotherapy. In the largest, mostly retrospective, patient series a more than 50% reduction in seizure frequency was observed in 44–77% of patients after irradiation or chemotherapy with temozolomide (13). LGG patients who received early radiotherapy more often showed seizure freedom after 12 months compared to patients who received late radiotherapy (75% *vs.* 59%) (14). Furthermore, patients with uncontrolled seizures may respond quickly to radio- or chemotherapy, even a few days or weeks after initiation of antitumor treatment (15). Other chemotherapeutic agents, including the combination of procarbazine, CCNU and vincristine (PCV), may contribute to a seizure reduction as well (16,17).

The occurrence of seizure control in patients with glioma not only depends on the resection, but is also influenced by factors related to tumor type, tumor status and its treatment and individual factors, which may be subject to change during the course of disease. Apart from symptomatic or localization-related epilepsy, the natural tendency of gliomas to recur as well as their infiltrative growth may cause an additional risk for seizure relapse (13,18). In comparison to GBM, patients with low-grade gliomas show a longer period before developing a pattern of fluctuating seizure control due to a longer survival (5). Nonetheless, it is still controversial whether seizure recurrence is directly related to tumor progression. In a retrospective study of 508 LGG patients undergoing resection, postoperative seizure relapse was not associated with tumor progression, whereas another series of 332 LGG patients reported a hazard ratio of 3.80 for tumor progression in case of seizure recurrence compared with ongoing seizure freedom (6,7).

Although the risk of seizure recurrence in glioma patients may vary during the course of disease, patients generally show a weaker response to AED treatment compared to the general epilepsy population (5). In addition, side effects are commonly observed, occurring in 20–40% of glioma patients, which might partly be attributable to enzyme-inducing AEDs such as phenytoin and carbamazepine, that may cause drug-drug interactions or interactions with chemotherapeutic agents or radiotherapy (19,20). As a consequence, there is currently a general consensus to avoid enzyme-inducing AEDs and to apply non-enzyme-inducing AEDs as levetiracetam, valproic acid and lately also lacosamide as first choice anticonvulsants (19,21,22). In glioma patients who achieve seizure freedom after tumor resection or other antitumor treatment, the question may arise whether AEDs can be withdrawn at some point, particularly when the patient experiences disturbing side effects. As there is little evidence available on its safety, AED withdrawal should be considered only in glioma patients with a favorable prognosis, who have achieved stable disease in combination with long-term seizure freedom (23).

Unfortunately, the study of Neal *et al.* suffers from a number of drawbacks. The most important one is that the authors have performed an analysis on the postoperative seizure course in gliomas without differentiating to the type of glioma. Low-grade gliomas (grade II), anaplastic astrocytomas (grade III) and high-grade gliomas or glioblastoma (GBM, grade IV) are treated as one group, while each has its own epilepsy characteristics with differences in presentation and frequency of seizures during follow-up. Besides, GBM is overrepresented with almost 60% of patients, while absolute numbers of grade II and III gliomas are small.

The course of postoperative seizures is divided up in grades A, B, C and D, of which the first three in fact represent all benign epilepsy courses. As course C receives the most attention, its definition is the more relevant as severity of the epilepsy is not accounted for, while most seizures in gliomas are partial ones not lasting longer than 30 seconds. Although the authors have performed multivariate analyses between tumor progression, defined as re-resection, and seizure course, they have not included tumor progression defined by receiving second line chemotherapy. Although alluded to in the discussion, one misses particularly an analysis on the relation between the time and potential of seizure recurrence and the timing of tumor recurrence. For those reasons the value of this paper relates mostly to the sub-analysis they performed on GBM, that is grade IV patients. On this group, the authors found that 48% of patients experienced postoperative seizure freedom with an even distribution in the remaining three epilepsy courses.

Overall, gliomas comprise a relatively heterogeneous group of brain tumors with a fluctuating seizure risk, depending on a wide range of factors including type of tumor, actual tumor status and its treatment. Neal *et al.* demonstrate the fluctuating course of seizures. Like many

other clinical reports on epilepsy in gliomas, the results of this study should be interpreted with caution due to its retrospective design and the strong heterogeneity of the study population. Future prospective studies are highly needed to overcome these weaknesses. Therefore, accurate prospective monitoring of seizures, AED treatment, antitumor treatment and radiological follow-up is essential, using uniform outcome measures (24). In that case, it may become possible to predict more precisely when seizures may occur during the course of disease.

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