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Risk factors for seizures and antiepileptic drug-associated adverse effects in high-grade glioma patients: A multicentre, retrospective study in Hong Kong

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Aim: The aim of this present study was to determine the frequency, as well as risk factors, for seizures and antiepileptic drug (AED)-associated adverse effects among high-grade glioma (HGG) patients.

Patients and Methods: A multicentre, retrospective study of adult Chinese Hong Kong patients from three neurosurgical centres diagnosed with supratentorial HGG between 1 January 2001 and 31 December 2010 was performed.

Results: A total of 198 patients, with a mean age of 55 years (range: 18–88) and a mean follow up of 15 months, was recruited. Most suffered from glioblastoma multiforme (GBM) (63 per cent) followed by anaplastic astrocytoma (25 per cent). Median overall survival for patients with GBM was 8 months, and 11 months for those with grade III gliomas. Prophylactic AED was prescribed in 165 patients (83 per cent), and 64 per cent of patients were continued until end of life or last follow up. A total of 112 patients (57 per cent) experienced seizures at a mean duration of 8 months postoperatively (range: 1 day–75 months). Independent predictors for seizures were a diagnosis of GBM [adjusted odds ratio (OR): 2.33, 95 per cent confidence interval (CI): 1.21–4.52] and adjuvant radiotherapy (adjusted OR: 2.97, 95 per cent CI: 1.49–6.62). One-fifth of patients (21 per cent) experienced AED adverse effects, with idiosyncratic cutaneous reactions and hepatotoxicity most frequently observed. An independent predictor for adverse effects was exposure to aromatic AED, such as phenytoin, carbamazepine and phenobarbital (adjusted OR: 3.32, 95 per cent CI: 1.32–8.40).

Conclusions: Antiepileptic drug prescription for primary seizure prophylaxis is both pervasive and prolonged for HGG patients. Seizures occur frequently, but most were delayed and none were life threatening. Judicious prescription of AED is required, especially when a significant proportion of patients experience adverse effects. Patients with a diagnosis of GBM and exposure to radiotherapy are at risk. We suggest, contrary to present practice, that primary seizure prophylaxis be given only during the perioperative period and resumed when they occur. We also recommend avoidance of aromatic AED due to their association with idiosyncratic adverse effects.

Key words: adverse effect, aromatic antiepileptic drug, glioblastoma multiforme, high-grade glioma, seizure prophylaxis.

Introduction

Seizures in brain tumor patients are a common phenomenon accounting for 20–40 per cent of cases.[1] The occurrence of seizures in patients with brain metastases is estimated to be between 15 and 25 per cent.[2] For high-grade malignant gliomas (HGG), the frequency is substantially higher, varying between 30 and 60 per cent.[2] One-third of glioblastoma multiforme (GBM) patients experience seizures at presentation, and a further 30 per cent suffer seizures later in the disease course.[3] Although there are clear indications

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for antiepileptic drug (AED) treatment for the general brain tumour patient presenting with seizures, several studies have confirmed that long-term primary prophylaxis is ineffective.[4] The American Academy of Neurology-issued practice parameter, based on a meta-analysis of four randomized, controlled trials, recommends against their routine prescription for all patients with newly-diagnosed brain tumours, regardless of pathology.[5] Data concerning perioperative seizure prophylaxis is less clear, and clinical trials focusing on its effectiveness in adults with HGG are limited. It is imperative to identify HGG patients at risk of developing seizures, but at present, convincing evidence is inadequate. The objectives of this retrospective study were to determine the incidence, as well as risk factors, for seizures and AED-associated adverse effects among this select group of patients.

Methods

Clinical and radiological data of consecutive patients with HGG diagnosed over an 11-year period, from 1 January 2001 to 31 December 2010, were analysed. Hospital inpatient and clinic records from three neurosurgical centres serving a population of 3.2 million were reviewed. Inclusion criteria were ethnic Chinese patients of 18 years or older with a histologically-proven supratentorial HGG, in accordance with the World Health Organization's (WHO) classification grades III or IV.[6] Exclusion criteria were patients who did not have the primary operation performed in the participating centres; had a pre-existing, unrelated seizure disorder; or received antiepileptic medication for an alternate purpose, such as neuropathic pain or bipolar affective disorder. Demographic data, seizure presentation, histologic subtype of HGG, tumour location, duration of prophylactic AED treatment, aim of the operative procedure (i.e. maximal safe resection or biopsy) and adjuvant oncological treatment, were compiled. Outcome measures were the occurrence and timing of postoperative seizures, defined as a seizure occurring after the primary operation until last clinical contact and AED-associated adverse effects. Adverse effects were classified according to the WHO: type A, reversible and dose dependent (e.g. ataxia, dizziness, drowsiness, and cognitive dysfunction); type B, idiosyncratic (e.g. skin reactions and hepatotoxicity); and type C, related to cumulative dose of the drug (e.g. decreased bone mineral density and weight changes).[7]

Statistical analysis was carried out using the Pearson's χ^2-test or Fisher's exact test to identify risk factors for AED-associated adverse effects and postoperative seizures. Patients who were alive at 30 June 2011 (i.e. a minimum of 6 months after the primary operation), or at last clinical contact, were censored. *P*-values less than 0.05 were considered statistically significant. All tests were performed using the Statistical Package for the Social Sciences programme version 16.0.1 (SPSS, Chicago, IL, USA).

Results

Patient characteristics and overall survival

A total of 241 were diagnosed as having a HGG in this 11-year period (Table 1); 198 eligible patients met the study criteria, with a male-to-female ratio of 1.6 to 1.

Table 1. Patient characteristics ($n = 198$)

Characteristic	*n* (per cent)
Sex, male : female	1.6:1
Age at tumour diagnosis, mean (SD and range), years	55 (15, 18–88)
Histology	
WHO grade IV (i.e. GBM)	125 (63)
WHO grade III	73 (37)
Anaplastic astrocytoma	49 (67)
Anaplastic oligoastrocytoma	8 (11)
Anaplastic oligodendroglioma	6 (8)
Gliosarcoma	5 (7)
Anaplastic ependymoma	5 (7)
Prior history of low-grade glioma	22 (11)
Tumour location	
Frontal	79 (40)
Temporal	53 (27)
Parietal	39 (20)
Occipital	10 (4)
Basal ganglia and thalamus	17 (9)
Preoperative AED prophylaxis	165 (83)
Phenytoin	91 (55)
Valproic acid	69 (42)
Phenobarbital	3 (2)
Carbamazepine	2 (1)
Duration of AED primary prophylaxis, mean (SD), months	12.3 (18.8)
Surgical treatment	
Biopsy	28 (14)
Maximal safe resection	170 (86)
Adjuvant treatment	147 (74)
RT	88 (60)
TMZ and RT	52 (35)
PCV/CCNU and RT	3 (2)
TMZ alone	4 (3)
Overall survival, median (SD), months	9.0 (10.8)
GBM	8.0 (7.8)
WHO grade III	11.0 (15.2)

AED, antiepileptic drug; CCNU, carmustine; GBM, glioblastoma multiforme; PCV, procarbazine–lomustine–vincristine; RT, radiotherapy; SD, standard deviation; TMZ, temozolomide; WHO, World Health Organization.

The mean age at tumour diagnosis was 55 years (18–88 years), and 40 per cent were older than 60. Most patients (81 per cent) had a preoperative Karnofsky functional performance score of 70 or greater. Ninety per cent of patients attended regular clinical follow up, with a mean duration of 15 months. Most underwent their primary operation with the aim of maximal safe tumour resection (86 per cent, 170 patients). Median overall survival for patients with GBM (i.e. WHO grade IV gliomas) was 8 months (range: 1–36 months), and 11 months (range: 1–69 months) for patients with grade III gliomas.

Tumour characteristics

The majority of tumours were GBM (63 per cent, 125/198 patients), and the remaining were WHO grade III gliomas, of which anaplastic astrocytoma (25 per cent, 45 patients) was predominant. Other grade III tumours, anaplastic oligoastrocytomas, anaplastic oligodendrogliomas and gliosarcomas constituted 10 per cent of HGG. The epicentres of most tumours were located in the frontal lobe (35 per cent, 70 patients) and in the temporal lobe (27 per cent, 53 patients). By 30 June 2011, tumour recurrence was observed in 84 per cent of GBM patients at a mean time of 6 months, and 80 per cent of WHO grade III glioma patients at a mean time of 14 months.

AED-prescribing patterns and adverse effects

A total of 165 patients (83 per cent) received preoperative prophylactic AED, and more than half were prescribed phenytoin (55 per cent, 91 patients) (Table 1). The second most-frequently prescribed AED was valproic acid (VAL) (42 per cent, 68 patients). A vast majority (98 per cent, 157 patients) was prescribed AED beyond 1 week postoperatively, with a mean treatment duration of 1 year (range: 5 days to 182 months). Almost two-thirds of patients (128 patients, 64.3 per cent) were on AED for the remainder of their lives or until last follow up. Among these patients with protracted AED administration, 51 (25.8 per cent) had no history of seizures. Seizures upon presentation (Fisher's exact test, $P = 0.569$), operation type ($P = 1.000$), GBM histology ($P = 0.298$) and tumour location were not associated with extended AED treatment beyond 1 week.

AED-associated adverse effects were noted among one-fifth of patients (21 per cent, 41 patients) with type B idiosyncratic hepatotoxicity and cutaneous reactions being the most common manifestations (Table 2). Two patients suffered from life-threatening Stevens–Johnson syndrome (SJS) and recovered. No mortality was ascribed to AED administration.

Table 2. Seizure occurrence and AED adverse effects

Characteristic	*n* (per cent)
Seizure as presenting symptom	47 (27)
Partial	21 (45)
Generalized	19 (40)
Secondary generalized	7 (15)
Postoperative seizure at 6 months	93 (47)
≤ 1 week	8 (9)
≤ 1 month	15 (16)
Breakthrough seizure	66 (33)
Seizure during entire disease course	112 (57)
Time from operation to first seizure, mean (SD), months	8.2 (11.9)
WHO AED-associated adverse effects classification	41 (21)
Type A: related to drug mechanism of action	
Drowsiness/cognitive impairment	3 (2)
Type B: idiosyncratic	
Cutaneous reaction	17 (9)
Hepatotoxicity	17 (9)
Myelosuppression	4 (2)
Type C: related to cumulative drug dose	0

AED, antiepileptic drug; SD, standard deviation; WHO, World Health Organization.

The only significant independent risk factor for adverse effects was a history of exposure to aromatic AED, such as phenytoin, phenobarbital and carbamazepine [adjusted odds ratio [OR]: 3.32, 95 per cent confidence interval [CI]: 1.32–8.40) (Table 3). There was no association with sex, patient age, AED polytherapy, the duration of AED administration or systemic chemotherapy.

Seizure presentation and occurrence

Almost one-quarter of patients presented with seizures (24 per cent, 47 patients), and the frequency of generalized versus focal seizures were comparable, occurring in 40 per cent and 45 per cent of patients, respectively (Table 2). More than half the patients developed seizures during the entire disease course (57 per cent, 112 patients), of which the majority (83 per cent, 93 patients) occurred postoperatively. More than half episodes (58 per cent, 66 patients) were breakthrough seizures, despite the patients being on AED. Only 9 per cent of patients developed seizures in the first postoperative week, and 16 per cent within 1 month. Most seizures were delayed at a mean duration of 8 months after the primary operation (range: 1 day–75 months).

Risk factors for postoperative seizures identified from univariate analysis included: histological diagnosis of GBM (OR: 1.91, $P = 0.031$), adjuvant radiotherapy

Table 3. Risk factors for AED adverse effects

Factor	No adverse effects ($n = 157$) *n* (per cent)	Adverse effects ($n = 41$) *n* (per cent)	Univariate		Multivariate	
			OR (95 per cent CI)	*P*-value	Adjusted OR (95 per cent CI)	*P*-value
Clinical features						
Male	100 (51)	23 (21)		0.372		
Age at tumour diagnosis, mean (SD), years	55 (15)	55 (14)		0.076		
AED					3.32 (1.32–9.40)	0.011
A-AED	100 (51)	35 (18)	3.33 (1.32–8.39)	0.008		
VAL	122 (63)	32 (41)	2.65 (1.18–5.92)	0.015		
Duration of PHT, weeks	60	48		0.499		
Duration of VAL, weeks	34	36		0.847		
AED polytherapy	17 (11)	4 (10)		0.322		
Adjuvant chemotherapy	37 (24)	12 (29)		0.439		

A-AED, aromatic antiepileptic drug; CI, confidence interval; OR, odds ratio; SD, standard deviation; PHT, phenytoin; VAL, valproic acid.

Table 4. Risk factors for seizures

Factor	No seizures ($n = 105$) *n* (per cent)	Seizures ($n = 93$) *n* (per cent)	Univariate		Multivariate	
			OR (95 per cent CI)	*P*-value	Adjusted OR (95 per cent CI)	*P*-value
Clinical features						
Male	59 (56)	64 (69)		0.068		
Age at tumour diagnosis, mean (SD), years	55 (15)	54 (15)		0.440		
Seizures on presentation	20 (19)	27 (29)		0.099		
Tumour features					2.33 (1.21–4.52)	0.012
WHO grade IV (i.e. GBM)	59 (56)	66 (71)	1.91 (1.06–3.44)	0.031		
Preceding LGG	12 (11)	10 (11)		0.880		
Tumour location				NS		
AED prophylaxis						
A-AED	61 (68)	53 (57)		0.875		
VAL	39 (37)	38 (41)		0.592		
Surgical treatment					2.87 (1.49–6.62)	0.001
Maximal safe resection	89 (85)	32 (78)		0.638		
Adjuvant treatment						
History of RT	79 (67)	77 (83)	2.41 (1.23–4.72)	0.014		
TMZ and RT	20 (19)	35 (38)	2.57 (1.35–2.88)	0.004		
Multiple craniotomies	38 (36)	42 (45)		0.129		
Tumour recurrence	72 (69)	84 (90)	2.98 (1.30–8.85)	0.008		
Overall survival, mean (SD) months	13.3 (8.7)	18.1 (14.5)		0.064		

A-AED, aromatic antiepileptic drug; CI, confidence interval; GBM, glioblastoma multiforme; LGG, low-grade glioma; NS, not significant; OR, odds ratio; RT, radiotherapy; SD, standard deviation; TMZ, temozolomide; VAL, valproic acid; WHO, World Health Organization.

(OR: 2.87, $P = 0.001$), adjuvant temozolomide (OR: 2.57, $P = 0.004$), and tumour recurrence (OR: 2.98, $P = 0.008$) (Table 4). A trend to significance was noted with longer clinical follow up ($P = 0.064$). Multivariate analysis revealed that independent significant predictors for postoperative seizures were a diagnosis of GBM (adjusted OR: 2.33, $P = 0.012$) and a history of adjuvant radiotherapy (adjusted OR: 2.87, $P = 0.001$). No association could be established with tumour location, history of preoperative seizures, history of low-grade glioma, surgical intention (maximal safe resection or biopsy) or multiple craniotomies. No significant difference was observed between the use of aromatic AED (i.e. phenytoin, phenobarbital or carbamazepine) and VAL. No deaths directly attributable to seizures were documented.

Discussion

HGG are the most common primary malignant central nervous system (CNS) neoplasms in adults and carry a poor prognosis.[8] Life expectancy is brief, with a median overall survival of 1–3 years.[8] Quality of life becomes an important issue for HGG patients and their caregivers. One principal source of morbidity is seizures along with its treatment-associated adverse effects. In the present study, 27 per cent of patients presented with seizures, and 57 per cent experienced them during the disease course. This is comparable to previous reports of 30 per cent and 60 per cent, respectively, among HGG patients.[2,3,9,10] It is likely that in view of the high occurrence of seizures, neurosurgeons from the participating centres prescribed prophylactic AED for 83 per cent of HGG patients, despite recommendations against their routine use.[5] This practice is commonly encountered worldwide, and according to the Glioma Outcomes Project, 57 per cent of patients in North America with newly-diagnosed HGG received seizure prophylaxis.[11] Similar guidelines suggesting that perioperative AED should be weaned off 1 week postoperatively for brain tumour patients are frequently not followed.[5] Our findings reveal that 98 per cent of HGG patients were on AED for more than a week after the operation, and were prescribed for almost two-thirds of patients until the end of life or last follow up. Again, this practice is not exceptional; another multicentre study observed that two-thirds of patients were prescribed AED for more than 1 week postoperatively.[1] Although the current study was not designed to assess the effectiveness of prophylactic AED, these findings reflect the concerns of local clinicians in mitigating seizure-associated sequelae in HGG patients. Despite these concerns, none of the patients suffered from life-threatening seizure complications, such as status epilepticus or sudden unexplained death in epilepsy.

On the contrary, the consequences of such pervasive and prolonged AED treatment – where a considerable number of patients (26 per cent) received medication until death or last follow up without ever experiencing a seizure – are its associated adverse effects.[1,12] Adverse effects were identified in 21 per cent of patients and is in keeping with reports of between 10 and 40 per cent of general epilepsy patients.[7] This retrospective review was dependent on spontaneous reporting with precise documentation, and it was discovered that only type A or B adverse effects were readily identifiable from the clinical records. Type C effects, although commonly occurring in 1–10 per cent of epilepsy patients, were not documented in any of the patients in this cohort.[7] It is believed that clinicians might have considered conditions, such as osteoporosis, body weight fluctuations, hirsutism, and alopecia, to be too insignificant to record, or they might have been less recognizable compared to the more overtly symptomatic type A and B effects.[7] It was also difficult to analyse drug-interaction adverse effects due to polypharmacy, including dexamethasone and various chemotherapeutic agents, often observed in HGG patients. There have been reports that enzyme-inducing AED might reduce overall survival due to their induction of P450 microsomal enzymes, resulting in enhanced metabolism of chemotherapeutic agents, but the findings are inconsistent, and class I evidence is lacking.[13–16] For the present study, the heterogeneity of oncological treatment regimens confounded analysis of effects of this nature.

Type A effects, such as drowsiness and cognitive impairment, although known to be occurring in over 10 per cent of patients, were far less observed, with only three patients (2 per cent) documented to have such symptoms.[7] It is believed that a degree of underreporting was involved, and this might be due to patient tolerance of such symptoms or that the clinician may have attributed such CNS complaints to the presence of a malignant brain tumour or radiation toxicity. In contrast, a relatively higher number of patients (9 per cent) suffered from type B idiosyncratic reactions compared to literature reports of their incidence being less than one per cent.[7] Nevertheless, the only independent risk factor for both types of adverse effects combined was the use of aromatic amine agents, namely phenytoin, phenobarbital and carbamazepine, with an adjusted OR of 3.32 (95 per cent CI: 1.32–9.40).

The aromatic benzene ring structure shared by these three commonly-prescribed AED is likely to be the cause for their propensity to develop idiosyncratic type B adverse effects.[7] Dermatological and hepatic reactions have been reported to occur twice as frequently with aromatic AED than with non-aromatic AED, such as VAL.[17] The exact pathogenesis is unknown, and several mechanisms have been proposed, including direct cellular damage by drug metabolites or immune-mediated hypersensitivity reactions.[7,18] The prevailing hypothesis favours the latter in light of several recent immunogenetic studies. Patients of Han Chinese ancestry have a predisposition for human leukocyte antigen (HLA)-B*1502 allele positivity, an inherited variant of the *HLA-B* gene, which is strongly associated with carbamazepine- and phenytoin-induced SJS and toxic epidermal necrolysis.[19] Such severe cutaneous adverse reactions are reportedly two-to-three times more prevalent

in Han Chinese than Caucasians.[20] Allelic positivity has been estimated to be strikingly variable among different ethnic groups, occurring in 10–15 per cent of individuals from southern China and other South–East Asian countries compared to less than 1 per cent in Japan and 0–0.1 per cent in European Caucasians.[21] Researchers have suggested that the same HLA-B allele variant could also account for phenytoin and carbamazepine hepatotoxicity in Chinese patients, but this remains to be validated.[22] Although data comparing phenobarbital-induced reactions and HLA-B*1502 status are limited, clinical cross-reactivity to an aromatic AED after a cutaneous reaction elicited by a drug of the same class has been reported to be as high as 60–70 per cent in Chinese people.[23] It would be prudent to avoid switching to other aromatic AED should significant idiosyncratic reactions arise, especially when alternative non-aromatic agents are available.

It is therefore pertinent to identify patients at risk of developing postoperative seizures for more discriminate AED administration, especially when median life expectancy is limited to less than 1 year. After accounting for confounding variables, the independent risk factors were the presence of GBM, with an OR of 2.33 (95 per cent CI: 1.21–45.52) and adjuvant radiotherapy ($P = 0.001$). The aggressive infiltrative nature of GBM has led to several proposed pathogenic mechanisms for seizure development, of which tumour necrosis, hemosiderin deposition, peritumoral hypoxia and cortical deafferentiation have been described.[24,25] Peritumoral glutamate excitotoxicity, as a result of increased glutamate synthetase activity in GBM tumour cells, compared to grade III glioma cells, is another posited seizure generation pathway.[26] Radiation toxicity is a well-known cause for iatrogenic seizures. According to the Radiation Therapy Oncology Group, any toxicity occurring 90 days after completion of radiotherapy is defined as a late effect.[27] The mean period for seizure occurrence was 8 months, and the association with radiotherapy suggests that late-onset radiation leukoencephalopathy might be an underlying cause for postoperative seizures rather than tumour recurrence. From a series of 352 GBM patients who received adjuvant radiotherapy, 28 per cent suffered from radiation-induced leukoencephalopathy.[28] Magnetic resonance imaging (MRI) was not routinely performed at the time of seizure occurrence, so it was difficult to ascertain this possibility in this cohort. However, the temporal relationship between delayed seizure occurrence and radiation toxicity implicated by these findings reflects that MRI evaluation in patients with postoperative seizures should be considered in future prospective studies.

Retrospectively reviewing patient outcomes introduces inherent limitations. Underreporting of type A CNS adverse effects, as well as the heterogeneous timing of AED treatment in relation to chemoradiotherapy, AED serum concentrations and its potential drug interactions, are factors that need to be addressed in prospective studies. Because routine HLA-B*1502 allele testing for patients on carbamazepine was only first introduced in 2007, data from this cohort were incomplete, especially for patients on similar aromatic class agents.[29]

Conclusion

This study confirms current literature that seizures occur frequently in patients with HGG, but we found that most were delayed, occurring months after the operation, and none were life threatening. Judicious prescription of AED is required, given that a significant portion of patients experience adverse effects, and that quality of life is crucial when overall survival is limited. Patients with a diagnosis of GBM and a history of radiotherapy are at risk; therefore, we suggest, contrary to present practice, that primary seizure prophylaxis be given only during the perioperative period and resumed when they occur. We also recommend avoidance of aromatic AED due to their association with idiosyncratic adverse effects, and suggest non-aromatic agents, such as VAL instead.

Declaration of conflict of interest

All authors declare that they have no conflicts of interest.

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