Original Article

JHSMR Journal of Health Science and Medical Research

Psychiatric Adverse Effects of Levetiracetam in Malignant Glioma Populations; a Retrospective Cohort Study

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Received 2 January 2021 ● Revised 16 February 2021 ● Accepted 21 February 2021 ● Published online 27 May 2021

Abstract:

Objective: Levetiracetam is commonly used in malignant glioma populations because of its efficacy, limited drug-drug interactions and adverse effects. Although, there has been growing evidence of adverse neuropsychiatric side effects from levetiracetam; however, such evidence in malignant brain tumor settings is limited. Hence, we hypothesized that malignant glioma patients exposed to levetiracetam would also experience more adverse neuropsychiatric effects compared to patients not receiving this medication.

Material and Methods: A retrospective cohort analysis was conducted in 150 high grade malignant glioma patients at our Cleveland Clinic Cancer Center; from 2013-2014, comparing the accumulative adverse neuropsychiatric outcomes between patients who received levetiracetam and patients who did not (n=108 and 42, respectively). A sub-analysis of each specific neuropsychiatric side effect between these two groups was performed.

Results: Patients with malignant glioma receiving levetiracetam had increased risk of developing neuropsychiatric adverse effects compared to the non-levetiracetam group (odds ratio=2.08, p-value=0.040, 95% confidence interval=1.00-4.36). After adjusting for confounding factors, past psychiatric history and the interaction between seizure and levetiracetam use was significantly associated with neuropsychiatric problems. Delirium, psychosis, and irritability were more common in the levetiracetam group, and likely led to more psychiatric referrals, starting of psychotropic medications, and vitamin B6 use.

Conclusion: Incidence of neuropsychiatric presentations in malignant glioma patients was higher in the levetiracetam exposed group than the non-exposed group. The changes, or emergence of new neuropsychiatric behaviors should prompt clinicians to search for possible causes; including levetiracetam adverse effects, so they can be managed accordingly.

Keywords: Drug-Related Side Effects and Adverse Reactions, glioma, levetiracetam, mental disorders

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J Health Sci Med Res .....
doi: 10.31584/jhsmr.2021814
www.jhsmr.org

Introduction

Many patients with central nervous system (CNS) tumors present with or experience seizures during the course of their illness.[1-3] Approximately 30.0% of patients with glioblastomas will have a seizure.[4,5] Antiepileptics; such as phenytoin and carbamazepine, are hepatic enzyme inducers and are generally avoided, if possible: due to the risk of decreased efficacy of chemotherapy.[6] This has led to the frequent use of non-enzyme inducers; such as levetiracetam, topiramate, and lamotrigine, in this patient population. Additionally,there has also been proposals to use enzyme inhibitors, such as valproic acid.[7,8] Due to levetiracetam's effective control of seizures, limited life-threatening side effects, simple regimen coupled with ease of administration (available in both intravenous and oral formulations), it has become one of the more commonly used anti-epileptic in brain tumor patient populations.[9]

It has been reported in previous literature that the prevalence of behavioral and psychiatric symptoms in glioma patients, such as depression, were approximately around 30.0-40.0%.[10-12] Concurrently, there has also been a growing understanding as well as appreciation of levetiracetam-induced behavioral changes.[13] Although, this phenomenon is most commonly seen in pediatric populations it has also been observed in adults.[14] Irritability, or even frank psychosis induced by levetiracetam greatly hinders the patient's quality of life; especially in terms of interpersonal relationships, making such effects highly undesirable.

We postulated that brain tumor patients, afflicted with gliomas, will be more susceptible to the adverse neuropsychiatric effects of levetiracetam. We also hypothesized that patients with high grade malignant gliomas (WHO III, IV) are at an increased risk of developing this adverse neuropsychiatric manifestation if receiving levetiracetam as an anti-epileptic.

Material and Methods

We performed a retrospective analysis of 150 glioma patients at the Cleveland Clinic Cancer Center; from 2013-2014. To meet the inclusion criteria, patients had to be aged 18 or older, have no active alcohol or illicit substance use, be diagnosed with high grade malignant gliomas (WHO grade III or IV), and had been followed at the Cleveland clinic for more than 6 months. Patients with low grade malignant gliomas or other benign/non-cancerous tumors; such as, meningioma, metastatic tumor, infectious granuloma, and spinal cord tumors, were excluded. The study group consisted of patients who received levetiracetam monotherapy for at least 3 months, or longer, as first line treatment for new onset seizures or seizure prophylaxis. The control group consisted of glioma patients who did not receive antiepileptic medication or received antiepileptic medications, other than levetiracetam. Demographic and clinical data from the electronic medical records were collected. The demographic data included the patients' age, gender, race, and marital status. Patients were stratified based on tumor type, grade, location, laterality, tumor recurrence, and treatment modalities. The primary outcome of this study was the total neuropsychiatric adverse reactions in both groups.

Evidence of neuropsychiatric adverse side effects were: referral for psychiatry consultation or psychiatric admission, new diagnosis of the neuropsychiatric problems; based on documented clinical diagnosis from the electronic medical records (depression, anxiety, irritability, mania, psychosis), starting on new psychotropic medications; such as antidepressants or neuroleptics, a discontinuation or change in antiepileptic; due to neuropsychiatric symptoms, or addition of vitamin B6; which is commonly used to alleviate behavioral adverse reactions, such as agitation and irritability.[15] All demographic and clinical factors were analyzed to find possible risk or risk reduction in occurrence

of neuropsychiatric problems. Categorical variables were demonstrated as frequency and percentage, while continuous variables were reported as mean and standard deviation. Both demographic and clinical data between the two studied groups were compared by Fisher's exact test for hypergeometric distribution.[16] Simple binary logistic regression was used to determine the possible risk factors of adverse neuropsychiatric outcomes.[17] All statistical parameters were analyzed by using SPSS version 17. This study was approved by Cleveland clinic's institutional review board, and followed the ethical research codes of the World Medical Association (Declaration of Helsinki). The authors received no funding source for this study.

Results

Nine hundred patients with CNS tumors that received treatment at the Cleveland Clinic Cancer Center; from 2013-2014, were identified by computer database query: 150 patients met the inclusion criteria. The majority of the patients excluded from this study were those with benign CNS tumors or CNS metastatic lesions. All patients in the final study population had a diagnosis of grade III or IV malignant glioma. One hundred and eight of them had received levetiracetam for at least 3 months, or longer. The average age of the study population was 55.5 (range=25–89 years). Most of the patients in this sample had no previous degenerative brain diseases or psychiatric disorders. However, 11.2% of the patients in the levetiracetam group alongside 21.4% of the patients in the non-levetiracetam group were reported to have past history of depression, anxiety, or other psychiatric illnesses. Glioblastoma multiforme was the most common histologic finding, followed by anaplastic astrocytoma, and anaplastic oligodendroma. Less than half (40.7%) of the patients' tumors were categorized as grade 3, and 59.3% were grade 4. Tumor locations most frequently found in this study were: Frontal, temporal, and parietal lobes. Most tumors were located in a single lobe; although fewer numbers of the tumors expanded across two or three lobes. In terms of laterality, the percentage of right, left, and bilateral tumors were 46.0, 49.3, and 4.7%, respectively. Approximately two-thirds of patients suffered from seizure episodes during the malignant glioma diagnosis, or initial surgical treatment period. The average levetiracetam dose range was 1,000-2,000 milligram per day. More than half of the patients (29 out of 42) from the non-levetiracetam group did not receive antiepileptic drugs, while the rest of the patients in this group were treated with some other drugs; such as valproic acid, lacosamide or lamotrigine. The major treatment modalities for brain tumors were surgical resection, chemotherapy, and radiation therapy. Occurrences of seizures before initiation of antiepileptic drugs, and tumor recurrence were both significantly higher in the levetiracetam group than in the control group. Other demographic and clinical parameters showed no significant difference between the two groups: as demonstrated in Table 1.

Table 2 demonstrated the crude odds ratio and p-value of total adverse psychiatric outcomes as well as the specific diagnosis of psychiatric problems found after initiation of antiepileptics. Patients with high grade malignant gliomas that received levetiracetam as an antiepileptic in this study had increased risk of developing adverse neuropsychiatric effects; with an unadjusted odds ratio of 2.08 (p-value=0.040, 95% confidence interval (CI)=1.00-4.36) compared to patients with similar tumor conditions not receiving levetiracetam.

Binary logistic regression was performed to explore the impact of other confounding factors that may be associated with neuropsychiatric adverse events. These factors included: age, gender, past psychiatric history, seizure history, tumor type, grade; and location as well as chronic steroid use. We found that a patients' past psychiatric history had the largest value in predicting adverse psychiatric effects; while age, gender, tumor

Table 1 The demographic and clinical data compared between the levetiracetam and non-levetiracetam groups

Characteristics	Levetiracetam N=108 (%)	Non-levetiracetam N=42 (%)	Total N=150	Fisher's exact tests for hypergeometric distribution (p-value)
Age (mean (S.D.))	54.4 (13.0)	58.6 (13.3)	55.5 (13.2)	0.700
Male	65 (60.2)	22 (52.4)	87	0.460
Female	43 (39.8)	20 (47.6)	63	
Caucasian	101 (93.5)	37 (88.1)	138	0.200
African-American	4 (3.7)	5 (11.9)	9	
Other	3 (2.8)	0 (0.0)	3	
Single	18 (16.7)	7 (16.7)	25	0.710
Married	70 (64.8)	29 (69.1)	99	
Divorced	15 (13.9)	6 (14.3)	21	
Widowed	4 (3.7)	0 (0.0)	4	
No past psychiatric history	96 (88.8)	33 (78.6)	129	0.120
Past psychiatric history	12 (11.2)	9 (21.4)	21	
Depression	6 (5.6)	4 (9.5)	10	
Anxiety	3 (2.8)	3 (7.1)	6	
Others	3 (2.8)	2 (4.8)	5	
No psychiatric family history	11 (10.2)	8 (19.1)	19	0.170
Psychiatric family history	97 (89.8)	34 (80.9)	131	
Glioblastoma multiforme	60 (55.6)	27 (64.3)	87	0.410
Anaplastic oligodendroglioma	19 (17.6)	3 (7.1)	22	
Anaplastic astrocytoma	19 (17.6)	7 (16.7)	26	
Others	10 (9.3)	5 (11.9)	15	
Tumor grade 3	46 (42.6)	15 (35.7)	61	0.470
Tumor grade 4	62 (57.4)	27 (64.3)	89	
No tumor recurrence	44 (40.7)	25 (59.5)	69	0.030
Tumor recurrence	64 (59.3)	16 (40.5)	80	
Frontal lobe	43 (39.8)	13 (31.0)	56	0.550
Temporal lobe	22 (20.4)	12 (28.6)	34	
Parietal lobe	18 (16.7)	5 (11.9)	23	
Other single lobe	3 (2.8)	6 (14.3)	9	
Two or Three lobes	22 (20.4)	6 (14.3)	28	
Right sided	52 (48.2)	17 (40.5)	69	0.190
Left sided	53 (49.1)	21 (50.0)	74	
Both sided	3 (2.7)	4 (9.5)	7	
No seizure	15 (13.9)	35 (83.3)	50	<0.001
Seizure	93 (86.11)	7 (16.7)	100	
No gamma knife	98 (90.7)	39 (92.9)	137	1.000
Gamma knife	10 (9.3)	3 (7.1)	13	
No chemotherapy	2 (1.9)	4 (9.5)	6	0.050
Chemotherapy	106 (98.1)	38 (90.5)	144	
No chronic steroid use	55 (50.9)	22 (52.4)	77	1.000
Chronic steroid use	53 (49.1)	20 (47.6)	73	

S.D.=standard deviation

Table 2 The crude odd ratio of accumulative and specific clinic outcomes between the levetiracetam and non-levetiracetam groups

Clinical outcome	Levetiracetam N=108 (%)	Non-Levetiracetam N=42 (%)	p-value	Crude odd ratio (95% confidence interval)
Need for discontinuation	15 (13.9)	-	-	-
Need for dose lowering	7 (6.5)	-	-	-
Need for switching antiepileptic drugs	13 (12.0)	-	-	-
Start vitamin B6	6 (5.5)	0 (0.0)	0.190	0.72 (0.65-0.79)
Start antipsychotic after levetiracetam use	5 (4.6)	2 (4.8)	1.000	0.94 (0.16-5.03)
Start antidepressant after levetiracetam use	32 (29.6)	9 (21.5)	0.420	1.48 (0.63-3.45)
New psychiatric consultation	29 (26.9)	8 (19.0)	0.410	1.50 (0.62-3.61)
All new psychiatric diagnosis	55 (51.0)	14 (33.3)	0.100	1.96 (0.93-4.15)
Delirium	4 (3.7)	0 (0.0)		
Psychosis	2 (1.9)	1 (2.4)		
Mania	1 (0.9)	0 (0.0)		
Depression	38 (35.2)	12 (28.6)		
Anxiety	12 (11.1)	7 (9.5)		
Irritability	17 (15.7)	1 (2.4)		
Others	2 (4.2)	0 (0.0)		
Total psychiatric outcome	58 (53.7)	15 (35.7)	0.040	2.08 (1.0004-4.3581)

characteristics, seizure history, and chronic steroid use did not have any significant effect. After including age, gender, past psychiatric history, seizure history; and levetiracetam use, we found that levetiracetam no longer significantly predicted adverse neuropsychiatric effects (adjusted OR=0.65, p-value=0.430, 95% CI=0.22–1.92); while past psychiatric history was the most significant risk factor (adjusted OR=7.91, p-value=0.001, 95% CI=2.27-27.61). However, when an interaction term between seizure history and levetiracetam use was added, it could predict a 4-fold increased risk of adverse neuropsychiatric events (adjusted OR=4.3, p-value=0.010, 95% CI=1.421–12.97).

Malignant glioma patients receiving levetiracetam appeared to have higher rates of new antidepressant use, new psychiatric consultations as well as new diagnoses of psychiatric conditions; including, delirium, depression, anxiety, and irritability. However, these differences did not reach statistical significance.

Discussion

This retrospective cohort study demonstrated a higher incidence of neuropsychiatric events in patients with malignant glioma who take levetiracetam. Levetiracetam increased the likelihood of having adverse neuropsychiatric outcomes compared to the non-levetiracetam group; with a crude OR of 2.08. After controlling for other potential confounding factors, past psychiatric history and the interaction term between seizure history and levetiracetam were associated with higher risk of adverse neuropsychiatric effects. Moreover, patients who were placed on levetiracetam had a tendency (although not statistically significant) to develop more frequent delirium, depression, anxiety, and

irritability as well as receiving vitamin B6 supplementation and psychiatric referrals.

Previous studies have attempted to find the association between levetiracetam use and emerging neuropsychiatric problems in various clinical settings. Chen et al[18] reported that psychiatric and behavioral side effects of levetiracetam in children with epilepsy was 16.2%, which was the highest among antiepileptic drugs. The systematic review of 727 patients using levetiracetam in children with epilepsy in 2014, showed a statistically significant, relative risk of 2.18 for developing behavioral side effects compared to a placebo[19]: this was comparable to the calculated risk of this study.

Initial case series, evaluating the use of the levetiracetam in brain tumor related seizures, indicated that this medication is safe and tolerable.[20,21] In contrast the studies of Belcastro et al.[22] and Bedetti et al.[23] in 2017, both reported a significant association between frontal lobe tumor location, levetiracetam treatment, and neuropsychiatric adverse events. However, the former study only focused on low grade brain tumors, while the latter study excluded patients with underlying psychiatric disorders and family history of psychiatric illnesses. The result of our work additionally support the association between levetiracetam and neuropsychiatric problems in brain tumor populations, and further extends the understanding of this association into the high grade/malignant tumor realm. Our study also highlighted that past psychiatric history, and the interaction between seizure and levetiracetam may further increase the odds of developing adverse neuropsychiatric issues in this population. In our cohort, patients who received levetiracetam had a significantly higher rate of seizures. Unsurprisingly, the interaction between seizure and levetiracetam might enhance the clinical susceptibility towards neuropsychiatric symptoms.

Depression, followed by irritability and anxiety were the most frequent psychiatric problems found in the malignant glioma patients who received levetiracetam. This is concordant with prior studies in epilepsy populations.[9,19,24,25] Psychosis and delirium occurred at lower incidence, which again did not differ from the previous reports.[26-29]

This study has several limitations; which impact its generalizability. The first limitation of this study is its small sample size. Due to the limitation of time and data accessibility, we were able to recruit only 150 patients that met the study criteria from the cancer database: 2013-2014. This limited the power of this study, and thus decreased the chance of finding a true association between levetiracetam use and neuropsychiatric effects. Secondly, the control group combined patients who were not exposed to any antiepileptics with patients who received antiepileptics other than levetiracetam, so as to increase the sample size of the group. Sodium valproate and lamotrigine were occasionally used in malignant glioma cases for seizure control, which may indirectly alleviate their affective problems stemming from several CNS derangements in the control group.[8]

Despite the attempt to control for confounding factors, we did not collect nor compare tumor growth rates. This may have led to different clinical and behavioral outcomes between the groups. In addition, this study did not use standard screening or diagnostic tools to identify neuropsychiatric effects, which may have impacted the accuracy of our outcome measurement. Finally, the primary outcome of our study used global psychiatric incidence, not a measured specific psychiatric outcome. A benefit of this method may have allowed us to measure a broad range of issues, and may be useful in finding a crude maximum incidence of adverse effects. However, one disadvantage is that this method decreases its specificity at the cost of sensitivity. Therefore, the primary outcome of this study could possibly be exaggerated from over-inclusion of some factors that may not have been a direct consequence of the levetiracetam.

Future research in this area should consider a larger prospective cohort design that compares levetiracetam with other antiepileptic drugs; such as valproic acid, lamotrigine, and carbamazepine, in malignant glioma patients. A different approach would be adding individuals who are placed on levetiracetam for other reasons as another control group, which may shed light on the complex nature of the relationship between levetiracetam and neuropsychiatric disturbances.

Conclusion

This study demonstrated a higher incidence of neuropsychiatric problems in patients with malignant glioma who received levetiracetam, when compared with those who did not. The adverse effects of this medication are likely prevalent in malignant glioma patients, because they suffer from a higher level of central nervous system vulnerability and damage. While levetiracetam has many advantages in its use for patients with brain tumors, cautious monitoring for potential neuropsychiatric side effects needs to be exercised. Further studies to elucidate the underlying mechanism, actual rate of incidence along with more specific management for this problem are required.

Acknowledgement

We appreciate the assistance of Dr. Napakwawat Buathong and Dr. Yanin Thipakorn, for the final manuscript reviewing. None of the contributors received compensation for their work.

Funding sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The Authors declare that there is no conflict of interest.

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