ANTICANCER RESEARCH *40*: 2059-2064 (2020)
doi:10.21873/anticanres.14163

Prolonged Steroid Dependence in Adult Patients With Glioma

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Abstract. *Background/Aim: Prolonged use of glucocorticoids (GC) in glioma treatment can lead to adrenal insufficiency (AI) and subsequent steroid dependence due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. This is challenging to diagnose due to its nonspecific clinical symptoms erroneously ascribed to treatment. This study aimed to evaluate the risk factors predisposing patients with gliomas to develop AI. Patients and Methods: Charts in the neuro-oncology clinic from July 2018 to March 2019 were reviewed. Inclusion criteria included >18 y/o with WHO Grade II-IV gliomas, and secondary AI. Demographic profile, tumor characteristics, and treatment profile were compared. Results: The majority of patients were started on high dose dexamethasone at >8 mg daily, and were on dexamethasone for 4-8 months. The minimum dose needed to prevent symptoms was 0.5 mg to 2 mg daily. The majority received standard radiation doses ranging from 54-60 Gy. Most patients had radiation exposure to the HPA axis within the prescription isodose levels. Conclusion: Prolonged steroid dependency can result from chronic GC use in patients with glioma. Dose and duration of GC are risk factors for its development. Radiation exposure to the HPA axis may also be a contributing factor.*

Glucocorticoids (GC) are a mainstay in the treatment of primary brain tumors. GC have been used for reducing vasogenic edema and improving symptoms related to swelling including: lethargy, headache, and nausea, among others. Dexamethasone is the commonly used GC for the treatment of central nervous system (CNS) tumors due to its potent anti-cerebral edema effects, long half-life, and low mineralocorticoid activity, hence minimizing fluid retention.

Despite their benefits, prolonged use of GC can have a number of negative consequences. One of the most commonly unrecognized symptoms is the development of adrenal insufficiency (AI) and subsequent steroid dependence due to the suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Clinically, this can present with a wide range of signs and symptoms, including weakness/fatigue, malaise, nausea, vomiting, diarrhea, abdominal pain, headaches, fever, anorexia/weight loss, myalgia, arthralgia, as well as psychiatric symptoms (1). Screening for AI includes measuring early morning cortisol at 8:00 AM after GC dose has been tapered to a physiologic dose, and holding any oral GCs the evening and morning prior to the test. If the morning cortisol is normal but clinical suspicion for AI is high, an adrenocorticotrophic stimulating hormone (ACTH), cosyntropin stimulation, test can be performed to clarify the diagnosis (1).

The challenge in diagnosing AI in glioma patients may stem from its nonspecific clinical presentation, and thus the tumor itself or the treatments (*e.g.* chemotherapy, radiation therapy) may be erroneously ascribed as the cause of these symptoms. Hence, GC use is often extended unnecessarily. In addition, there are no guidelines on the dosing, duration, and tapering of GC in neuro-oncologic patients, and therefore the decision to discontinue use and tapering of doses is based primarily on the individual physician's discretion or the MRI results, which do not always correlate with neurologic symptoms. Current data on the incidence of AI in primary brain tumors is limited, particularly for gliomas (2). The role of external beam radiation therapy (EBRT) in the development of AI, including dose and proximity to the hypothalamus and the pituitary gland, is also not clearly established (3). This retrospective case series of ten glioma patients evaluates the risk factors that predispose patients with gliomas to developing AI and steroid dependency during the treatment course of their

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Key Words: Adrenal insufficiency, secondary adrenal insufficiency, steroid dependence, glioma, glioblastoma.

gliomas, including tumor location and molecular profile, dose and duration of dexamethasone use, as well as radiation dose and its proximity to the hypothalamus and the pituitary gland.

Patients and Methods

This is a retrospective case series review of patients treated in the Neuro-Oncology clinic at UT Southwestern (UTSW) Medical Center from July 2018 to March 2019. A total of 313 patient charts were reviewed. Inclusion criteria included >18 years old, diagnosis of glioma, WHO Grade II to IV, and a diagnosis of secondary AI by either morning cortisol level, ACTH, or symptoms of steroid withdrawal with resolution of symptoms following cortisol replacement under the care of an endocrinologist. The demographic profile, tumor characteristics (location, molecular markers), radiation history (dose, exposure or proximity to hypothalamus and pituitary gland), current treatment (concurrent or adjuvant temozolomide, bevacizumab infusion, or active surveillance), as well as dexamethasone dose and total duration of treatment of the cohort patients were all collected and compared.

Table I. *Basic demographic profile and glioma characteristics of the cohort.*

Demographic	N=10
Age (Mean, Range)	52.9 (39-64) yrs.
Gender (n)	
Male	6
Female	4
Type of glioma (n)	
Glioblastoma (WHO Grade IV)	5
Anaplastic astrocytoma (WHO Grade III)	2
Diffuse oligodendroglioma (WHO Grade II)	1
Gliosarcoma (WHO Grade IV)	1
Glioma NOS	1
Location (n)	
Frontal	5
Parietal	1
Temporal	2
Brainstem	2
Treatment at presentation(n)	
Adjuvant temozolomide	7
Bevacizumab infusion	1
Surveillance imaging	2

Results

A total of ten patients were identified who met the inclusion criteria. Diagnosis of AI was made through laboratory findings (low morning cortisol, ACTH) or clinical suspicion of AI, with subsequent referral and treatment of AI managed by an endocrinologist either at UTSW Medical Center, or at an outside facility. The demographic profile of the cohort is presented in Table I. Ages ranged from 39-64 years old, with a slight male preponderance (60%). Most had a diagnosis of WHO grade IV glioblastoma or grade IV gliosarcoma. Tumor location was most commonly the frontal lobe. The majority of patients had received active therapy during presentation of symptoms (80%). Two patients were off treatment and are currently on active surveillance.

MRI upon diagnosis of AI; these patients received thorough neurologic examinations to exclude the likelihood that their symptoms were primarily attributed to tumor progression or treatment effects. All patients received dexamethasone. Nine of the ten patients were started on a high dose of dexamethasone (>8 mg daily), and one patient was started on a lower dose (<4 mg daily) at initial dosing. The majority of the patients were on dexamethasone for less than a year (4-8 months), while 4 of the patients remained on dexamethasone for longer than 2 years, with one patient on steroids for a total of 64 months (Figures 1 and 2). The minimum required dose of dexamethasone ranged from 0.5 mg to 2 mg daily. Further tapering down of this dose range led to development of symptoms, the most common of which was fatigue, along with generalized weakness and headaches. Other symptoms experienced by the patients include weight loss, loss of appetite, nausea and lightheadedness (Figures 1 and 2).

Of the ten patients, one had abnormal morning cortisol level at 3.0 mcg/dl, while three patients had low normal morning cortisol levels, between 6-9 mcg/dl (Figure 3). All four patients were off dexamethasone, with one patient on Hydrocortisone at 5 mg daily. Their morning cortisol levels were drawn between 7-9 AM. One patient had a low ACTH level, while two patients had low normal ACTH levels, based on the reference range at UTSW (Figure 3). Three patients did not have their HPA axis tested; however, they had been treated by an endocrinologist and were switched to hydrocortisone taper due to clinical suspicion of AI. One patient's lab tests were unavailable from an outside facility.

Patients received standard radiation doses with the majority having received 60 Gy to the postoperative bed and/or gross tumor with margin. The radiation oncologist reviewed the treatment plan of each patient to determine involvement of the HPA. Six patients were noted to have involvement of the HPA axis within the prescription isodose levels (Table II). Eight of the ten patients were eventually switched from dexamethasone to hydrocortisone, whereas two patients weaned off GC completely. All of the patients in the cohort reported interval improvement of their symptoms after steroid replacement therapy (Table II).

Discussion

The prevalence of secondary AI in adult patients with gliomas is unknown. Endocrine deficiency is better documented in the pediatric brain tumor population, and growth hormone (GH) deficiency is the most well documented adverse effect (4-6).

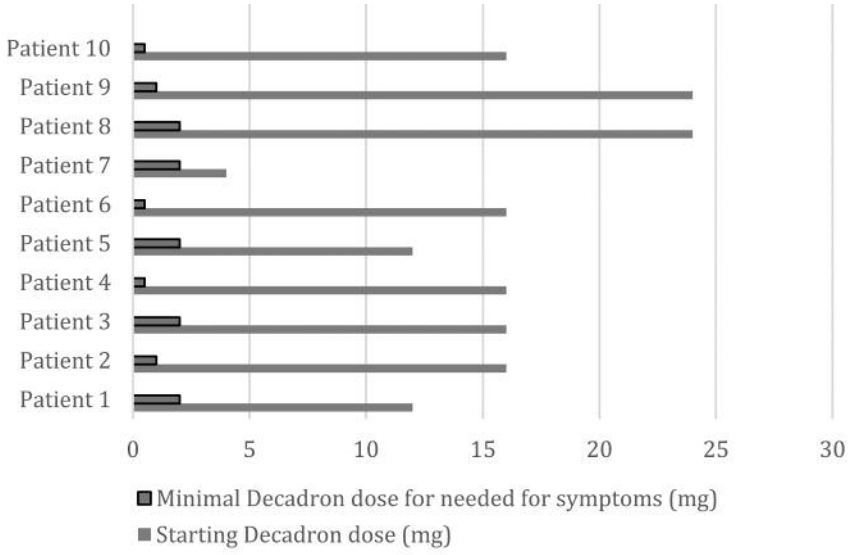

Figure 1. *Starting Decadron dose & minimal dose for adrenal insufficiency (AI) symptom relief*.

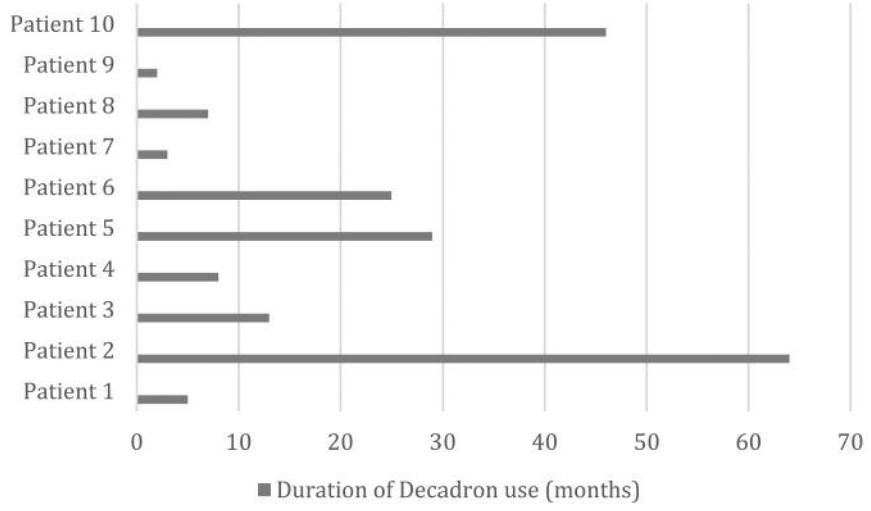

Figure 2. *Duration (in months) of Decadron use*.

Table II. *Endocrine management, radiation doses, and involvement of HPA*

Cohort	Endocrine Management	Improvement	Radiation dose	Involvement of HPA
Patient 1	Hydrocortisone 10/5 mg BID	Yes	60 Gy	Yes
Patient 2	Hydrocortisone 15/10 mg BID	Yes	60 Gy	Yes
Patient 3	Hydrocortisone 40/40/30 TID	Yes	60 Gy	Yes
Patient 4	Longer Dexamethasone taper	Yes	60 Gy	No
Patient 5	Hydrocortisone 30 QD	Yes	59.4 Gy	No
Patient 6	Hydrocortisone 15/5 mg BID	Yes	60 Gy	No
Patient 7	Hydrocortisone 10 mg	Yes	54 Gy	Yes
Patient 8	Hydrocortisone 5 mg QD	Yes	59.4 Gy	Yes
Patient 9	Longer Dexamethasone taper	Yes	60 Gy	Yes
Patient 10	Hydrocortisone 10/5 mg BID	Yes	60 Gy	No

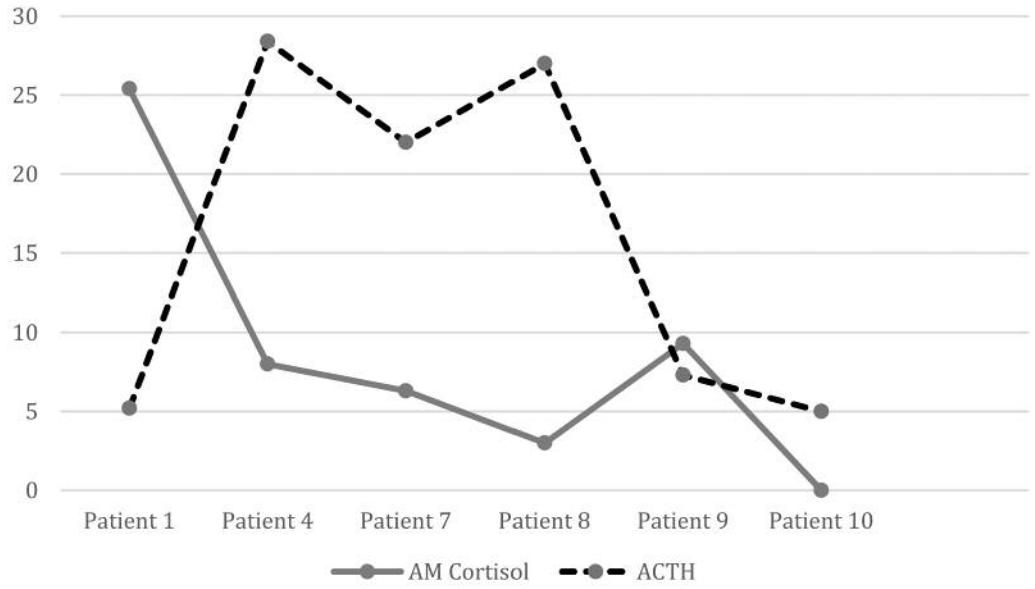

Figure 3. *AM cortisol and ACTH levels.*

In the adult population, there are no prospective studies on the development of HPA dysfunction based on serial endocrine testing, so most of the data are derived from retrospective reviews and meta-analyses (7). To our best knowledge, this is the first study highlighting secondary AI exclusively on glioma patients. There are similar studies that have included gliomas among other brain and skull-based tumors in their cohort, but none that focuses entirely on gliomas.

A systematic review by Joseph *et al.* has examined the influence of GC dose and duration of use on the prevalence of GC-induced AI. Of the 3,166 patients from 673 articles, only 3 patients were on GC for a nervous system indication. The results of their study showed that AI was demonstrated at <5 mg prednisolone equivalent dose/day, and <4 weeks exposure, and a cumulative dose of <0.5 g, and following tapered withdrawal (8). Since our cohort received dexamethasone, the prednisolone dose equivalence was evaluated for comparison. In our cohort, the patient that was started on the least amount of steroid received an equivalent of 25 mg of prednisolone daily. The majority of the patients in our cohort received at least 75 mg of prednisolone equivalent daily when they were first diagnosed with glioma. With regards to duration, the patients in our cohort were on GC for at least 4 months. It is therefore not surprising, based on this data, that our patients developed AI. Although Joseph *et al.* have concluded that answering their research questions was difficult given the heterogeneity of studies and variability of results, there is evidence that AI can occur in patients who are on GC for various diagnoses, and even at low doses and shorter duration of use.

A similar meta-analysis performed by Leonie *et al.* included the route of administration and disease in the stratification in addition to treatment dose and duration (9). The study concluded that the percentage of AI varied from 2.3% for those on low doses of GC to 21.5% prevalence for those on high doses. According to treatment duration, the percentage of AI was 1.4% if the treatment duration was <28 days, and up to 27.4% for >1 year. It is unknown how low or high doses of GC were defined in their study. The prevalence of AI was highest in patients with hematologic malignancies (60%), but none of the studies included brain tumor patients.

A study by Benghiat *et al.* has evaluated the prevalence of GC-induced AI in a specific cohort of 51 patients with brain and skull base tumors, and identified the factors predicting its occurrence (2). Most of the patients in their cohort had gliomas, accounting for 61% of the total patient population, with 20 (39%) of them diagnosed with low grade gliomas, and 11 (22%) with high grade gliomas. They concluded that the duration of and total exposure to dexamethasone (mg/days) were significantly associated with AI, additionally supporting the results of our study. A smaller case series study by Da Silva *et al.* has presented a cohort of 5 patients with brain tumors who developed AI after GC withdrawal. The prevalence of AI in their cohort was about 1%. The duration of steroid use in their cohort ranged from 1-14 months, and the doses were generally low in all patients. Their findings support that at even low doses and shorter duration of GC use, AI can still arise and should be considered as a cause of neurologic symptoms typically

erroneously attributed to increased intracranial pressure and side effects of radiation and chemotherapy (10).

In addition to the dose and duration of GC use, the role of radiation, including the dose and involvement of the HPA axis, may influence the risk of developing of AI. All patients in our cohort received a dose of 54 to 60 Gy of EBRT over a period of 6 weeks. The majority of the patients had some radiation exposure to the HPA axis based on the location of the tumor and treatment field. It is known that endocrine dysfunction is a common late effect of radiation in children and adults with brain tumors (3). However, there is very limited data on the presence of a dose response association. A study by Vatner et al has collected data on 222 brain tumor patients, both children and young adults <26 years old, treated with radiation in three prospective studies. They examined multiple endocrine deficiencies, including ACTH. Fourteen of the patients (7.4%) had a diagnosis of low-grade glioma. Their study showed that the incidence of hormone deficiency was highest among patients who received a hypothalamic and pituitary median dose greater than or equal to 40 Gy, with a 4-year actuarial rate of 6.9% for ACTH (3). Thus, radiation is also likely a contributing factor to the development of AI. Interestingly, a systematic review by Taku *et al*. has reported that HPA dysfunction occurred in 21.6-64.7% of patients with non-pituitary intracranial neoplasms. Their cohort included gliomas, although the exact percentage of the total population was unknown. In this study, there was no statistically significant association between the distances of the tumor to the HPA axis (7).

One of the main challenges in the study is the lack of highly accurate serum markers to support the diagnosis of secondary AI. All 10 study patients were referred to an endocrinologist due to clinical suspicion of AI. Their MRIs were stable at the time of referral, and their current dexamethasone dose, between 0.5 mg-2 mg daily, was too low to have significant anti-edema effect. In addition, although most of our patients were on some systemic treatment (*e.g*. temozolomide, bevacizumab), tapering off GCs had worsened their symptoms. The reintroduction of low dose GC allowed patients to return to their baseline level of function, further increasing clinical suspicion of secondary AI. Only one of our patients had a low morning cortisol level at 3.0 mcg/dl, while three patients had low normal morning cortisol levels, between 6-8 mcg/dl. The sensitivity of serum cortisol levels is poor at 60%; hence, a normal cortisol value does not rule out the presence of AI and will need further testing (1). Tests such as the ACTH stimulation test are performed to confirm AI (11). Only one of our study patients had the stimulation test with results within normal range. Due to persistent symptoms, this patient was switched to hydrocortisone and was eventually able to be tapered off of GC. Three of our patients had low ACTH; however, a low ACTH is also not a highly accurate assessment of the function of the HPA axis in secondary AI (12). Despite the lack of a concrete biochemical evidence of secondary AI, the low cortisol levels, low or normal ACTH levels, as well as the demonstration of symptom improvement upon reintroduction of steroids in the setting of stable MRI findings are supportive of a diagnosis of secondary AI.

A syndrome of steroid withdrawal may also be considered for our cohort patients. This syndrome is defined as an objective syndrome resembling true adrenal insufficiency and characterized by fever, anorexia, nausea, lethargy, malaise, arthralgia, desquamation of the skin, weakness, and weight loss in patients undergoing steroid withdrawal in the presence of biochemical evidence of HPA system integrity (13, 14). Earlier case studies have described this phenomenon. A study by Amatruda *et al*., has described a cohort of 10 male patients with pulmonary tuberculosis who were receiving prednisone and zinc corticotropin (ACTH) in addition to their systemic treatment. They found that despite gradual tapering of steroid dose, patients developed symptoms of AI, which responded to prednisone therapy. However, their plasma cortisol levels and response to ACTH were normal (15). A more recent study by Saracco *et al*. has evaluated the signs and symptoms of steroid withdrawal syndrome in children with acute lymphoblastic leukemia (ALL), comparing the difference between prednisone and dexamethasone. Their study showed that withdrawal symptoms can occur even with a 9-day taper schedule, and that symptoms were more frequent and severe in the dexamethasone group as compared to the prednisone group. It is interesting to note that while part of steroid withdrawal syndrome's definition is the presence of biochemical evidence of HPA system integrity, the majority of their patient population had HPA suppression, whereas only 37.1% of the prednisone group and 28.6% of the dexamethasone had an intact HPA (13).

All of the patients in our cohort were subsequently switched to hydrocortisone, which is more similar to the physiologic GC produced by the adrenal glands, or a longer taper of the dexamethasone, with improvement of their symptoms. Although there was a lack of laboratory support defining AI in our patients, there is clearly a GC dependency of iatrogenic etiology in our patients. Whether this is an atypical form of AI given the lack of laboratory findings supporting diagnosis, or steroid withdrawal syndrome, or even an operational definition of prolonged steroid dependency, more studies need to be performed to better characterize this phenomenon.

Conclusion and Future Directions

Secondary AI, as well as steroid withdrawal syndrome or prolonged steroid dependency, can result from chronic glucocorticoid use in patients with glioma. Correctly identifying

these syndromes are paramount to clinicians, as continued prolonged high dose steroid use has long-term consequences, including iatrogenic Cushing's syndrome, diabetes, osteopenia, *etc*. Automatically ascribing such symptoms erroneously to the brain tumor or its treatments would likely result in far more prolonged treatment with dexamethasone than is necessary. Given the dismal prognoses of many malignant glioma patients, quality of life issues are paramount to their optimal care, particularly when dealing with the side effects of GC. Both dose and duration of GC are risk factors for its development. Radiation exposure to the HPA axis may also be a contributing factor to the development of secondary AI in patients with glioma, although it can also occur in patients who had brain radiation distant from the HPA. More prospective studies need to be performed to better assess the relationship between radiation location and secondary AI, as the prevalence of secondary AI in the glioma population is likely underreported. Awareness of this condition is crucial for better management of these patients and eventually establishing evidence-based guidelines in the management of GC in patients with glioma.

Conflicts of Interest

All Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

Dr. Mantilla gathered data and is the primary author of the manuscript. Dr. Abramowitz contributed her expertise in Endocrinology. Dr. Dan contributed his expertise in Radiation Oncology. Dr. Pan is the team leader and is the main editor of the manuscript.

Acknowledgements

Dr. Emmanuel Mantilla's fellowship was partially funded by an educational grant from AbbVie pharmaceuticals.

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Received February 3, 2020
Revised March 8, 2020
Accepted March 9, 2020