

Review Article

Post-Traumatic Gliomas in Adults: Review of the Case Reports and Studies

Morgan Heinzelmann  and Edward Pan 

Department of Neurology, UT Southwestern Medical Center, Dallas, TX, USA

ABSTRACT: Traumatic brain injury (TBI) was first proposed as a potential risk factor for developing a glioma in the 1800s, and conditions for establishing a causal relationship between brain injury and gliomas have since been proposed. Given the medical and legal ramifications, the current literature was reviewed to better understand this possible association. Articles that examined the relationship between TBI and glioma formation in adults and were published in English between 1978 and 2022 were reviewed. There were 19 case reports of 25 patients and 16 observational studies. The case reports describe glioma formation at the precise site of prior brain injury in continuity with traumatic scar; the observational studies report conflicting findings, but they largely demonstrate no association. Most of the observational studies are limited by their retrospective nature, but we identified one prospective cohort study which found a positive association. Altogether, we suggest that glioma formation after TBI is a rare occurrence that warrants further study.

RÉSUMÉ : Gliomes de nature post-traumatique chez l'adulte : une revue des rapports de cas et des études portant sur le sujet. C'est dans les années 1800 qu'on a suggéré pour la première fois que les lésions cérébrales traumatiques pouvaient être un facteur de risque potentiel dans le développement d'un gliome. Depuis cette époque, on a tenté de déterminer les conditions permettant l'établissement d'une relation causale entre ces mêmes lésions et les gliomes. Compte tenu des implications médicales et juridiques en jeu, nous avons examiné la littérature médicale actuelle afin de mieux comprendre cette possible association. Nous nous sommes ainsi penchés sur des articles portant sur la relation entre les lésions cérébrales traumatiques et la formation de gliomes chez les adultes, articles qui ont été publiés en anglais entre 1978 et 2022. Au total, 19 rapports de cas portant sur 25 patients et 16 études d'observation ont été recensés. Les rapports de cas décrivaient la formation de gliomes exactement là où une lésion cérébrale antérieure s'était produite dans la continuité de la cicatrice traumatique. Les études d'observation, quant à elles, ont fait état de résultats contradictoires mais ont largement démontré l'absence d'association. Ajoutons que la plupart des études d'observation sont limitées par leur nature rétrospective ; cela dit, nous avons pu identifier une étude de cohorte prospective ayant établi une association positive. Dans l'ensemble, nous suggérons donc que la formation de gliomes à la suite d'une lésion cérébrale traumatique est un phénomène rare qui mérite une étude plus approfondie.

Keywords: Traumatic brain injury; Neurotrauma; Glioma; Post-traumatic glioma

(Received 11 January 2022; final revisions submitted 22 February 2022; date of acceptance 12 March 2022; First Published online 18 May 2022)

Introduction

Brain tumors represent a diverse group of neoplasms. They can be primary, originating from various cells within the central nervous system (CNS), or secondary, having metastasized from a systemic malignancy outside of the CNS. Furthermore, they can be either benign or malignant. The most common primary malignant brain tumor is glioblastoma (GBM). GBM is an aggressive grade IV glioma in the tumor family that originates from astrocytes, a type of glial cell. Glioma types include astrocytomas and oligodendrogliomas. There are risk factors that have been conclusively shown to affect risk of gliomas, such as ionizing radiation and genetic syndromes,¹ and there are a number of potential causative factors that require further investigation, with traumatic brain injury (TBI) being one such factor.

TBI was first proposed as a potential risk factor for the development of glioma by Virchow in 1864.² Since then, the notion that TBI predisposes an individual to developing an intracranial tumor, both benign and malignant, has been a topic of debate and controversy for many years. Opinions were based largely on case reports, until Parker and Kernohan “reopened the discussion” with the first case-control study of 431 glioma cases in 1931.³ Following this, numerous case reports and observational studies have been published, but the opinions regarding the idea of TBI increasing risk of gliomas remain quite polarized. Because there are significant pathogenic and medicolegal implications of asserting whether a glioma developed secondary to trauma, it became necessary to delineate criteria as to what constituted a causal relationship

Corresponding author: Morgan Heinzelmann, MD, Administrative Chief Resident, Department of Neurology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Suite G2.222, Dallas, TX 75390, USA. Email: morgan.heinzelmann@phhs.org

Cite this article: Heinzelmann M and Pan E. (2023) Post-Traumatic Gliomas in Adults: Review of the Case Reports and Studies. *The Canadian Journal of Neurological Sciences* 50: 365–372. <https://doi.org/10.1017/cjn.2022.31>

© The Author(s), 2022. Published by Cambridge University Press on behalf of Canadian Neurological Sciences Federation.

between TBI and subsequent development of brain tumor. In 1974, Zulch reviewed the literature and put forth the following conditions for a causal relationship⁴:

1. The patient must have been in good health before suffering the head injury.
2. The blow must be severe enough to cause brain contusion and a secondary reparative process.
3. The location of the impact and the tumor should correspond exactly one to the other.
4. There should be a time interval between trauma and the appearance of the tumor of at least 1 year, a longer latent period increasing the likelihood of a causal relationship.
5. The presence of the tumor must be proved histologically.
6. Trauma should consist of an external force.

Manuelidis then delineated three additional criteria for a causal relationship in 1978⁵:

1. The traumatized brain must also be proved histologically.
2. Bleeding, scars, and edema secondary to the presence of the tumor must be clearly differentiated from that caused by trauma.
3. Tumor tissue should be in direct continuity with the traumatic scar, not merely in its vicinity or separated by a narrow zone of healthy or slightly altered brain tissue.

With defined criteria, authors were held to these standards when publishing case reports. As the seventh criteria suggests, the only way to reliably distinguish post-traumatic glioma from previously normal brain parenchyma is to have histologic confirmation of the absence of tumor at the time of TBI. Traumatized brain is not routinely sent for histological examination, so this criterion is not feasible to adhere to. With the advent of contrasted CT and MRI neuroimaging techniques, Moorthy et al. suggested the addition of radiologic criteria.⁶ The authors recommended that neuroimaging should be used in the following three instances: (1) at the time of injury to demonstrate significant TBI, (2) shortly after resolution of TBI to demonstrate no evidence of intracranial mass, and (3) at the time of brain tumor diagnosis to demonstrate tumor development at the exact site of prior TBI.

The existing literature primarily consists of anecdotal case reports, as well as several case-control studies and a few cohort studies. While many of these studies have reviewed aspects of the pertinent literature, there has not been a comprehensive review encompassing all of both case reports and observational studies. This review includes the literature published from 1978 to present, as 1978 was the year that Manuelidis finalized the criteria necessary to demonstrate a causal relationship between TBI and glioma.

Materials and Methods

In order to obtain a comprehensive pool of studies that investigated and reported the potential association between TBI and subsequent development of glioma, PubMed was systematically searched using the following terms: concussion, head trauma, neurotrauma, brain injury, TBI, post-traumatic, brain tumor, brain malignancy, brain neoplasm, intracranial tumor, intracranial malignancy, intracranial neoplasm, astrocytoma, oligodendroglioma, glioma, and GBM multiforme. Additionally, each key word was cross-referenced with each other. The search included studies that (1) were published from 1978 to January 2022, (2) were

written in English, (3) were conducted in adults, and (4) reported or investigated the potential relationship between TBI and gliomas. Brain tumors other than gliomas, such as brain metastases and meningiomas, were excluded from this review.

All studies, with the exception of a few which were limited to the abstracts, were reviewed. For the case reports, variables of interest included patient demographics (age, gender), mechanism of injury (blunt injury by object, fall, motor vehicle accident, penetrating injury by object), type of brain injury (contusion, skull fracture, penetrating craniocerebral injury, intracerebral hemorrhage, subarachnoid hemorrhage), surgical intervention at the time of TBI, latency between TBI and glioma diagnosis, location of TBI/glioma, and type of glioma. For the observational studies, variables of interest included the study type, number of cases, TBI definition, tumor type(s), and findings. There were many early studies that were published in German, which are not reviewed here but are referenced by Stendel et al.⁷ This review did not require Institutional Review Board approval.

Results

Case Reports

We identified 19 case reports describing 25 patients who were diagnosed with gliomas after TBI (Table 1).^{2,6-23} About 77% of the patients were male. At the time of initial TBI, the average age of the patients was 41 (ranging from 17 to 66). At the time of glioma diagnosis, the average age of the patients was 55 (ranging from 29 to 68). The average latency period between TBI and glioma diagnosis was 15 years (ranging from 2 to 48 years). The TBIs included contusions, skull fractures, bleeds, and penetrating craniocerebral injuries. We also recorded the presence or absence of penetrating craniocerebral injury and surgical intervention, as these processes significantly disrupt the brain parenchyma. Eight patients had neither a penetrating craniocerebral injury nor surgical intervention at the time of injury, and 15 patients had either penetrating craniocerebral injury, surgical intervention at the time of injury, or both. This was unable to be determined for two patients due to review restricted to abstract only or because it was not reported. The location of the initial TBI and subsequent glioma formation occurred in both hemispheres (64% in left hemisphere) and in all cerebral lobes (most commonly in frontal lobes, 50%). Most of the patients, 66%, were diagnosed histologically with GBMs. Most of the others were diagnosed with anaplastic astrocytomas, and three patients had low-grade gliomas (two grade II oligodendrogliomas and 1 grade II astrocytoma that subsequently transformed into a grade III anaplastic astrocytoma on repeat biopsy).

Observational Studies

We identified 16 observational studies that sought to investigate the relationship between TBI and malignant brain tumors: 11 case-control studies and 5 cohort studies (Table 2). Many of these studies examined numerous risk factors and the development of various types of malignant brain tumors, but our discussion focused on the findings relating specifically to TBI and gliomas.

There were 13 observational studies that found no association between TBI and glioma formation, with 9 being case-control studies and 4 cohort studies. Of the case-control studies, only one focused solely on the risk of having had a head injury prior to diagnosis with glioma. Wrensch et al. surveyed 476 adults with newly diagnosed gliomas about their history of head injury.²⁴ Compared to controls, the odds ratio (OR) for having had a head

Table 1: Case reports

Study	Age	Gender	Mechanism	Brain injury	Penetrating injury	Surgical intervention	Latency (years)	Location	Tumor
Mrowka et al., 1978⁸	-	-	Penetrating injury by object	Penetrating craniocerebral injury	Yes	-	30	Left parietal lobe	Grade IV GBM
Troost et al., 1984⁹	-	-	Penetrating injury by object	Penetrating craniocerebral injury	Yes	-	40	-	Grade III anaplastic astrocytoma
Perez-Diaz et al., 1985 ²	58	Male	MVA	Contusion	No	No	28	Right frontal lobe	Grade II oligodendroglioma
	61	Male	Blunt injury by object	Contusion	No	No	7	Left frontal lobe	Grade II oligodendroglioma
Di Trapani et al., 1996 ¹⁰	47	Male	Blunt injury by object	Contusion	No	No	9	Left temporoparietooccipital lobe	Mixed grade II and III glioma (oligo and astro)
Stendel et al., 1997 ⁷	67	Male	Penetrating injury by object	Penetrating craniocerebral injury	Yes	Yes	48	Right frontal lobe	Grade IV GBM
Sabel et al., 1999 ¹¹	55	Male	Penetrating injury by object	Penetrating craniocerebral injury	Yes	No	37	Left frontal lobe	Grade IV GBM
Henry et al., 2000 ¹²	57	Male	MVA	Contusion, subarachnoid hemorrhage	No	Yes	2	Left temporal lobe	Grade IV GBM
Henderson et al., 2000¹³	-	-	-	Intracerebral hemorrhage	-	Yes	19	Left frontal lobe	Grade III anaplastic astrocytoma
Magnavita et al., 2003 ¹⁴	40	Male	MVA	Contusion	No	No	4	Right temporoparietal lobe	Grade IV GBM
Moorthy et al., 2004 ⁶	58	Male	MVA	Contusions (bilateral)	No	No	5	Left frontal lobe	Grade IV GBM
Salvati et al., 2004 ¹⁵	54	Female	MVA	Intracerebral hemorrhage	No	Not reported	7	left temporal lobe	Grade IV GBM
	68	Female	Fall	Skull fracture, contusion	Yes	Not reported	5	Left parietal lobe	Grade III anaplastic astrocytoma
	61	Female	MVA	Intracerebral hemorrhage	No	Yes	7	Left frontal lobe	Grade III anaplastic astrocytoma
	67	Male	MVA	Subdural hemorrhage	No	Yes	4	Left frontal lobe	Grade IV GBM
Anselmi et al., 2005¹⁶	40	Male	MVA	Intracerebral hemorrhage	-	-	20	Right parietal lobe	Grade IV GBM
	60	Male	MVA	Contusion	-	-	15	-	Grade IV GBM
Zhou et al., 2010 ¹⁷	45	Male	MVA	Intracerebral hemorrhage	No	No	10	Right temporal lobe	Grade IV GBM
Coskun et al., 2011 ¹⁸	65	Male	Blunt injury by object	Skull fracture, cerebral laceration	Yes	Yes	35	Left frontotemporoparietal lobe	Grade IV GBM
Han et al., 2013 ¹⁹	29	Female	MVA	Skull fracture, intracerebral hemorrhage	Yes	Yes	9	Right frontal lobe	Grade IV GBM
Spallone et al., 2013 ²⁰	37	Male	Not reported	Intracerebral hemorrhage	No	Not reported	20	Left posterior paraventricular region	Grade II–grade III anaplastic astrocytoma
Tyagi et al., 2016 ²¹	65	Male	Fall	Contusion	No	No	11	Left frontal lobe	Grade IV GBM
	54	Male	MVA	Contusion	No	Yes	7	Right frontal lobe	Grade IV GBM
Siminska et al., 2018 ²²	68	Female	Fall	Contusion, unspecified bleed	No	No	2	Right parietal lobe	Grade IV GBM
Juskys et al., 2020 ²³	47	Male	Fall	Intracerebral hemorrhage	No	Yes	4	Left frontotemporoparietal mass	Grade IV GBM

The **bold font** specifies studies that were not available for full review; “-” indicates that the information is not available from the abstracts.

Table 2: Observational studies

Study	Years of data collection	Study type	Age group	Number of cases (number of gliomas)	TBI definition	Tumor types	Results
Annegers et al., 1979 ³³	1935–1974	Cohort (retrospective)	Adult	2953 [1]	Head injury with brain involvement manifested by loss of consciousness, amnesia, or skull fracture	Astrocytomas, meningiomas	Negative
Hochberg et al., 1984 ³⁷	1977–1981	Case-control	Adult	[160]	Well-described concussion or brief loss of consciousness without any of the listed complications, as well as other inadequately described head trauma (mild), those resulting in a skull fracture or concussion and followed by a complication such as coma, intracranial hemorrhage, epilepsy, shock, or a long-lasting impairment of memory, hearing, or vision (severe)	Astrocytomas, GBMs	Positive
Burch et al., 1987 ²⁷	1979–1982	Case-control	Adult	[215]	Accidents and injuries with head involvement +/- medical attention	Astrocytomas, anaplastic astrocytomas, gemistocytic astrocytomas, pilocytic astrocytomas, GBMs, giant cell GBMs, malignant gliomas, mixed gliomas, oligodendrogliomas, microgliomas, unspecified	Negative
Carpenter et al., 1987 ²⁸	1943–1979	Case-control	Adult	[82]	Head injury	Astrocytomas, GBMs	Negative
Preston-Martin et al., 1989 ³⁰	1980–1984	Case-control	Adult	272 [202]	All head injuries occurring before reference year (2 years before the year of diagnosis of the case) that led to loss of consciousness, dizziness, or a medical consultation	Gliomas, meningiomas	Negative
Ryan et al., 1992 ³¹	1987–1990	Case-control	Adult	170 [110]	Head injury	Gliomas, meningiomas	Negative
Schlehofer et al., 1992 ³²	1987–1988	Case-control	Adult	226 [-]	Head injury	Primary brain tumors	Negative
Zampieri et al., 1994 ²⁹	1986–1988	Case-control	Adult	[195]	Head trauma that had caused only a brief change in consciousness (mild), head trauma that led to a loss of consciousness for more than 1 hour, neurological deficits, epilepsy, cranial fracture or any neurosurgical procedure (severe)	Medulloblastomas, ependymomas, oligodendrogliomas, low-grade astrocytomas, anaplastic astrocytomas, GBMs,	Negative
Inskip et al., 1998 ³⁴	1977–1993	Cohort (retrospective)	Adult	228,055 [113]	Concussion, contusion, cerebral laceration, skull fracture	Gliomas, meningiomas, embryonal tumors, neurilemmomas, vascular tumors, other	Negative
Hu et al., 1998 ³⁸	1989–1995	Case-control	Adult	[218]	Trauma to the head requiring medical attention	High-grade gliomas	Positive
Preston-Martin et al., 1998 ²⁵	1984–1992	Case-control	Adult	1509 [1178]	Head injury (mild), medically treated head injuries causing loss of consciousness, loss of memory, or requiring hospitalization that occurred 5 years before diagnosis (severe)	Gliomas, meningiomas	Negative
Wrench et al., 2000 ²⁴	1991–1994	Case-control	Adult	[476]	Head injury	Gliomas	Negative
Nygren et al., 2001 ³⁵	1965–1994	Cohort (retrospective)	Adult	311,006 [not reported]	Skull trauma	Primary brain tumors (astrocytomas, GBMs, ependymomas, ependymoblastomas, juvenile astrocytomas, oligodendrogliomas, neuroblastomas, neurofibrosarcomas, malignant meningiomas, medulloblastomas, acoustic neuromas, neurinomas, spongioblastomas, malignant schwannomas), meningiomas, other	Negative

(Continued)

Table 2: (Continued)

Study	Years of data collection	Study type	Age group	Number of cases (number of gliomas)	TBI definition	Tumor types	Results
Monteiro et al., 2006 ²⁶	1999–2002	Case-control	Adult	231 [31]	Head injury that had occurred at least a year prior to the brain tumor diagnosis; detailed severity markers such as hospitalization, loss of consciousness, and amnesia	Gliomas, meningiomas, other	Negative
Chen et al., 2012³⁹	2001–2002	Cohort (prospective)	Adult	5007 [9]	Traumatic brain injury requiring ambulatory care of hospitalization	Malignant brain tumors (not otherwise specified)	Positive
Munch et al., 2015 ³⁶	1978–2011	Cohort (retrospective)	Adult	48,194 [14]	Structural brain injury including traumatic brain injury, cerebral ischemic infarction, and spontaneous intracerebral hemorrhage	High-grade gliomas	Negative

The **bold font** specifies studies that were not available for full review; “–” indicates that the information is not available from the abstracts.

injury in glioma cases was 1.3 (CI 1.0–1.7), and the OR for having had a head injury which required medical attention was 1.1 (CI 0.8–1.4). Thus, head injury with or without medical attention was not an important contributor to the risk of glioma formation. Two other studies investigated head injuries as a risk factor, but they included meningiomas in addition to gliomas. Preston-Martin et al. investigated whether there was increased risk of tumor formation after head injuries, including sports-related head injuries, in 1509 adults.²⁵ Specific to gliomas in men, they found that the risk for ever having experienced any head injury was 1.2 (CI 0.9–1.5) and severe head injury was 1.1 (CI 0.7–1.6). This is one of two studies that investigated sports-related head injuries, and interestingly, there was a trend toward an inverse association between sports participation 5 or more years before diagnosis and risk of glioma formation. The other study was conducted by Monteiro et al. of 231 adults.²⁶ For the glioma cases, they found the risk of having experienced head injury that occurred at least a year prior to brain tumor diagnosis was positive but not statistically significant (OR 1.30, CI 0.71–2.35).

Three case-control studies examined the association of a myriad of risk factors, including brain injury and glioma formation. Burch et al. investigated 215 adults diagnosed with various types of gliomas.²⁷ More cases than controls reported accidents or injuries with head involvement (relative risk 2.51, $p < 0.0001$), but there was not a significant difference when exposure was limited to those that required medical attention (RR 1.20, $p = 0.65$). The authors suggested that this discrepancy was likely due to recall bias, given that the significance disappeared when restricted to injuries requiring medical attention, which are thought to be less prone to recall bias. Carpenter et al. also focused primarily on gliomas, including astrocytomas and GBMs, and their association with prior head injury.²⁸ They identified 82 patients but did not find an association between reported prior head injury and brain tumor (OR 0.9, CI 0.2–4.2); for gliomas specifically, the OR was 1.4 (CI 0.3–7.2). A study by Zampieri et al. included 195 patients diagnosed with various types of gliomas and asked about their history of mild or severe head trauma, but there was not a significant association (OR, CI 0.3–1.4).²⁹

Three case-control studies investigated head injury among a number of other risk factors in patients with primary brain tumors not limited to gliomas. Preston-Martin et al. interviewed 272 men with a glioma or meningioma about history of head injury occurring 2 years prior to their tumor diagnosis that led to loss of

consciousness, dizziness, or a medical consultation.³⁰ While they found a significant association for meningiomas, this risk was not significant for glioma development no matter the latency period or number of injuries (OR 0.8, CI 0.5–1.3). Ryan et al. also investigated adults with a diagnosis of glioma or meningioma and inquired about their history of head injury.³¹ The risk for having had a prior head injury in those with gliomas was not significant at 1.07 (CI 0.45–2.56). Lastly, Schlehofer et al. conducted a population-based study in Germany to investigate several risk factors for the development of primary brain tumors and found no significant association with head injury.³²

In addition to the negative case-control studies above, there are four cohort studies that did not find an association between TBI and glioma. Annegers et al. performed one of the earliest observational studies, a retrospective cohort analysis of 2953 adult patients in Minnesota who suffered and survived a “head injury with brain involvement manifested by loss of consciousness, amnesia, or skull fracture.”³³ The patients were subsequently followed for a total of 29,859 person-years. They identified four patients who developed brain tumors, three of which were meningiomas and one of which was an astrocytoma. The one astrocytoma did not differ significantly from the expected number of astrocytomas, based on age-specific incidence rates for brain tumors in the local population per one of their earlier studies. Inskip et al. conducted another retrospective cohort study of 228,055 Danish adults who were hospitalized for concussion, contusion, skull fracture, or cerebral laceration.³⁴ The patients were then followed for 8 years on average after injury and were evaluated for development of benign or malignant intracranial tumors. Gliomas, specifically, occurred at higher than expected rates during the first year after injury (standardized incidence ratio (SIR) 3.9, CI 2.7–5.5), but the authors suggested the likelihood for head trauma to have caused these tumors that grew rapidly enough to be diagnosed within 1 year was low. When excluding the first year after injury in accordance with the criteria proposed by Zulch and Manuelidis, the risk of developing a glioma was not significant (SIR 1.0, CI 0.8–1.2). Nygren et al. sought to explore the association between various diagnoses related to skull trauma and brain tumor development through a retrospective cohort study of 311,006 patients contributing to 3,225,317 person-years of follow-up in Sweden.³⁵ They identified a total of 281 cases and found that there was no association between TBI and overall risk of primary brain tumors (SIR 1.0, CI 0.9–1.2), nor in subgroup analyses of tumor type, age, year of follow-up, and

severity of brain injury. Lastly, based on the hypothesis that any condition causing astrogliosis could lead to development of an astrocytic tumor, Munch et al. performed a retrospective cohort study of 404,812 adults in Denmark who had experienced any structural brain injury, including TBI (48,194), cerebral ischemic infarction, or spontaneous intracerebral hemorrhage.³⁶ 6152 patients ultimately developed a high-grade glioma, either a grade III anaplastic astrocytoma or GBM, 14 of which were after TBI. There was no significant association after a structural brain injury between 1 and 4 years post-injury (RR 1.14, CI 0.87–1.46), and surprisingly, there was a significant protective effect of structural brain injury after 5 years (RR 0.68, CI 0.49–0.90). For TBI only, the risk of glioma development was 1.99 between 1 and 4 years (CI 1.00–3.50) and 0.32 after 5 years or more (CI 0.10–0.75).

There were three studies that found positive associations between TBI and glioma, two of which were case-control studies. Hochberg et al. published a case-control study of 160 adults with high-grade gliomas in the Boston area.³⁷ Data were collected by questionnaire and telephone interview, and patients were asked about whether they had sustained either a mild or severe head injury prior to tumor development. They found that there was an association between formation of high-grade glioma after head injury, but only in those who sustained a severe injury at age 15 or older (RR 10.6, CI 2.1–53.3). Hu et al. performed a case-control study of risk factors for 281 adults with high-grade gliomas in China.³⁸ They found that trauma to the head requiring medical attention was associated with increased risk of glioma (OR 4.09, CI 2.51–10.31).

There was one cohort study that found a positive association between TBI and development of malignant brain tumor. Furthermore, this is the only prospective cohort study to our knowledge. Chen et al. conducted this prospective cohort study of 5007 adults in Taiwan who had sustained a TBI requiring ambulatory care or hospitalization.³⁹ The patients were then followed for 3 years after injury to assess the risk of developing a malignant brain tumor. Within 3 years of surveillance, patients were more likely to develop a malignant brain tumor than controls, with risk being 4.67 times greater (CI 1.84–11.83). There was also an association between brain injury severity and malignant brain tumor ($p = 0.033$).

Discussion

Since the idea was first proposed, TBI as a potential risk factor for glioma development has been a controversial topic, particularly when considering the medicolegal implications. In an effort to better elucidate this relationship, we reviewed the pertinent literature between 1978 and 2022 and identified 19 case reports (detailing 25 patient cases) and 16 observational studies (11 case-control studies, 5 cohort studies). To our knowledge, ours is the first comprehensive review of both case reports and observational studies.

The 19 case reports detailed a total of 25 patient cases in which a glioma formed at the exact site of prior TBI. Demographically, this was observed in a wide range of adult ages; of note, glioma formation after TBI has also been observed in children, but those studies were not reviewed here.^{40–44} Cases were also observed in patients of both genders. Over 75% of the patients were male, which may represent a differential trend between genders or reflect the increased risk of TBI in males. According to the TBI Model System National Database Statistics from 2017, males accounted for 73% of TBIs reported.⁴⁵

Among the cases described, patients were diagnosed histologically with grade II, III, or IV gliomas, with 88% of the tumors being high-grade tumors; there were only three cases of low-grade gliomas after TBI, and one of the cases was reclassified as a high-grade glioma after a repeat biopsy, which may have reflected tumor progression or initial sampling error. Glioma formation occurred after a variety of TBI mechanisms, including contusions, skull fractures, hemorrhages, and penetrating craniocerebral injuries. One proposed explanation is that there may be neoplastic proliferation of “initiated” cells from disruption of the blood-brain barrier or cerebrovascular architecture by a penetrating foreign object or surgical instrumentation. Consistent with this proposed mechanism, 15 patients did have a penetrating craniocerebral injury and/or surgical intervention at the time of injury, but interestingly, glioma formation was reported in 8 patients that had not sustained either invasive event. The latency period between TBI and glioma diagnosis ranged widely from 2 to 48 years. According to the proposed guidelines for a causal relationship, there should be a time interval of at least 1 year, but given the aggressive nature of GBMs, it is reasonable that the number of cases reported in the literature may be underestimated through timing exclusion. Gliomas form in both hemispheres and all cerebral lobes. The most common location is the frontal lobe, which may correlate with the fact that the frontal lobe is particularly vulnerable to injury due to its large size and the bony prominences of the front of the skull.⁴⁶

Of the 16 observational studies identified, there were 11 case-control studies and 5 cohort studies, with conflicting negative and positive findings. There were 13 observational studies (9 case-controls, 4 cohorts) that found no association between TBI and glioma formation, while 3 observational studies (2 case-controls, 1 cohort) found such an association. These observational studies, and in turn our systemic review, have several limitations. First, these studies are limited by their retrospective nature, predisposing them to recall bias as many of these studies relied on patient recall on questionnaires; patients with brain tumors may be more likely to recall and report any head trauma than control patients. Furthermore, many studies used review of records to determine details of prior brain injury, which often did not clearly report mechanism, severity, and location of brain injury, further predisposing these studies to misclassification bias. This limitation of data collection makes it difficult to determine the extent to which the cases adhered to the Zulch and Manuelidis criteria, such as demonstrating that the location of injury impact and tumor corresponded. On a similar note, it is important to recognize the advent of CT and MRI neuroimaging around the same time that these criteria were being proposed and updated. However, it was not until 2004 that Moorthy et al. proposed radiologic criteria for demonstrating the absence of glioma at the time of injury and the development of glioma at the exact site of prior TBI. Some of the observational studies, although published in 1978 or later, used data that were collected in years prior and did not have neuroimaging to establish the absence of glioma at the time of TBI. The advancements in neuroimaging modalities over time may have also increased the likelihood of identifying neuropathology in later studies. Lastly, all observational studies have small sample sizes, largely due to the rarity of gliomas.

The lone prospective study found a positive association between TBI and glioma, a 4.67 times greater risk of developing a malignant brain tumor within 3 years of TBI, as well as an association between TBI severity and development of a malignant brain tumor.³⁹ Despite the larger number of observational studies that found no association, this prospective cohort study had the highest level of evidence. Methodologically, they utilized a nation-wide registry,

allowing for a large, population-based study (>98% of the Taiwanese population) and longitudinal follow-up. Furthermore, their registry requires biopsy and histological verification in order to make a definite diagnosis of brain malignancy. However, several limitations of this should be noted. First, this study was a population-based study in Taiwan, which may not allow the results to be generalizable. Second, there was no active surveillance during the follow-up period for the TBI and control groups; thus, there is the possibility of ascertainment bias, such that patients with persistent TBI-related symptoms may have received more neuroimaging during the follow-up period and thus were more likely to have brain malignancy detected. Third, the study used an arbitrary 3-year follow-up period; it is possible that their findings are underestimated given that malignant brain tumors may have a longer latency. Lastly, the authors report the diagnoses of “malignant brain tumor” but do not further specify histopathological or molecular classification which would be helpful to note.

Given these inconsistent findings and study limitations, additional research is required to better elucidate the relationship between TBI and development of glioma. The ideal study design would be a large, prospective cohort study in which TBI patients would be identified and followed for subsequent development of glioma. This would allow for accurate and precise documentation of the brain injury, and the observed incidence would be compared to the incidence of glioma in the general non-TBI population. Another approach would be to focus research efforts on identifying the possible mechanism by which glioma formation from prior TBI occurs. Thus far, there have been several proposed mechanisms for oncogenic transformation. One possible mechanism suggests that the inflammatory response following structural TBI may predispose to tumor formation by cellular proliferation beyond normal repair; chronic inflammation is a predisposing factor in other solid tumors such as GI malignancies.²¹ Another proposal is Knudson’s two-hit hypothesis, having inherited a loss of one copy of a tumor suppressor gene with TBI leading to the second “hit”.¹¹

Another interesting consideration is the possible interpretation of these studies in the context of sports-related TBI, particularly as this has become an increasingly popular topic in the medical community and popular culture. Every published case report described a moderate to severe injury prior to glioma formation, in which there was evidence of skull fracture, contusion, hemorrhage, and/or penetrating injury. These severe injuries are rare occurrences in sports-related TBI, which is typically considered a “milder” form of TBI (i.e., concussion). Sports-related head injuries were investigated in two of the observational studies, both of which found no association.^{25,34} While there are no case reports or observational studies to suggest a link between sports-related TBI and glioma formation, it is worth noting that repetitive “mild” sports-related TBI has been linked to a different neurologic process called chronic traumatic encephalopathy (CTE) that presents with neuropsychological symptoms. CTE is a progressive neurodegenerative disorder that is characterized by perivascular deposits of tau, proposed to occur in the setting of acceleration-deceleration mechanism leading to axonal injury, breakdown of the blood-brain barrier, neuroinflammation, and ultimately hyperphosphorylation of tau.⁴⁷

Conclusions

Dr Harvey Cushing once commented, after struggling with a post-traumatic meningioma in General Leonard Wood, that brain tumors after head trauma occurred “too often to be ignored.”⁴⁸

While these sentiments were in regard to a nonmalignant brain tumor, review of the literature of post-traumatic glioma reveals numerous case reports of the development of glioma at the precise site of prior severe TBI in continuity with traumatic scar. Although there are conflicting positive and negative findings in regard to his association in the observational studies, these studies have significant limitations from which definitive conclusions cannot be made. Overall, we suggest that glioma formation after TBI is a rare occurrence, but is certainly possible. This is an important association to better elucidate as it relates to patient care and legal ramifications. Future directions could include investigating which patients may be at highest risk for glioma formation after TBI.

Statement of Authorship. MH contributed to the concept for the manuscript, the systematic search of articles, the review of the literature, the manuscript writing, and the final approval for submission. EP provided expert mentorship and contributed to critical review of the manuscript, the manuscript editing, and the final approval for submission.

Disclosures. MH has nothing to disclose. EP has nothing to disclose.

References

- Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of glioma. *Nat Clin Pract Neurol*. 2006;2:494–503.
- Pérez-Díaz C, Cabello A, Lobato RD, Rivas JJ, Cabrera A. Oligodendrogliomas arising in the scar of a brain contusion. Report of two surgically verified cases. *Surg Neurol*. 1985;24:581–6.
- Parker HL, Kernohan JW. The relation of injury and glioma of the brain. *JAMA*. 1931;97:535–40.
- Zulch KJ, Mennel HD. The biology of brain tumors. In: *Handbook of clinical neurology*. Amsterdam: North-Holland; 1974, pp. 31–3.
- Manuelidis EE. Glioma in trauma. In: *Pathology of the nervous system*. New York: McGraw-Hill; 1972, pp. 2237–40.
- Moorthy RK, Rajshekhar V. Development of glioblastoma multiforme following traumatic cerebral contusion: case report and review of literature. *Surg Neurol*. 2004;61:180–4.
- Stendel R, Théallier-Jankó A, Höll T, Brock M. The relationship between cortical injury and brain tumour. Report of two cases and review of the literature. *Acta Neurochir*. 1997;139:208–14.
- Mrówka R, Boguńska C, Kulesza J, Bazowski P, Wencel T. Grave cranio-cerebral trauma 30 years ago as cause of the brain glioma at the locus of the trauma particulars of the case. *Zentralbl Neurochir*. 1978;39:57–64.
- Troost D, Tulleken CA. Malignant glioma after bombshell injury. *Clin Neuropathol*. 1984;3:139–42.
- Di Trapani G, Carnevale A, Scerrati M, Colosimo C, Vaccario ML, Mei D. Post-traumatic malignant glioma. Report of a case. *Ital J Neurol Sci*. 1996;17:283–6.
- Sabel M, Felsberg J, Messing-Jünger M, Neuen-Jacob E, Piek J. Glioblastoma multiforme at the site of metal splinter injury: a coincidence? Case report. *J Neurosurg*. 1999;91:1041–4.
- Henry PT, Rajshekhar V. Post-traumatic malignant glioma: case report and review of the literature. *Br J Neurosurg*. 2000;14:64–7.
- Henderson RD, Campbell SF. Head trauma and brain tumours revisited. *J Clin Neurosci*. 2000;7:262–4.
- Magnavita N, Placentino RA, Mei D, Ferraro D, Di Trapani G. Occupational head injury and subsequent glioma. *Neurol Sci*. 2003;24:31–3.
- Salvati M, Caroli E, Rocchi G, Frati A, Brogna C, Orlando ER. Post-traumatic glioma. Report of four cases and review of the literature. *Tumori J*. 2004;90:416–9.
- Anselmi E, Vallisa D, Bertè R, Vanzo C, Cavanna L. Post-traumatic glioma: report of two cases. *Tumori J*. 2006;92:175–7.
- Zhou B, Liu W. Post-traumatic glioma: report of one case and review of the literature. *Int J Med Sci*. 2010;7:248–50.
- Coskun S, Coskun A, Gursan N, Aydin MD. Post-traumatic glioblastoma multiforme: a case report. *Eurasian J Med*. 2011;43:50–3.

19. Han Z, Du Y, Qi H, Yin W. Post-traumatic malignant glioma in a pregnant woman: case report and review of the literature. *Neurol Med Chir.* 2013;53:630–4.
20. Spallone A, Izzo C, Orlandi A. Posttraumatic glioma: report of a case. *Case Rep Oncol.* 2013;6:403–9.
21. Tyagi V, Theobald J, Barger J, et al. Traumatic brain injury and subsequent glioblastoma development: review of the literature and case reports. *Surg Neurol Int.* 2016;7:78.
22. Simińska D, Kojder K, Jeżewski D, et al. The pathophysiology of post-traumatic glioma. *Int J Mol Sci.* 2018;19:2445.
23. Juškys R, Chomanskis Ž. Glioblastoma following traumatic brain injury: case report and literature review. *Cureus.* 2020;12:8019.
24. Wrensch M, Miike R, Lee M, Neuhaus J. Are prior head injuries or diagnostic X-rays associated with glioma in adults? The effects of control selection bias. *Neuroepidemiology.* 2000;19:234–44.
25. Preston-Martin S, Pogoda JM, Schlehofer B, et al. An international case-control study of adult glioma and meningioma: the role of head trauma. *Int J Epidemiol.* 1998;27:579–86.
26. Monteiro GTR, Pereira RA, Koifman RJ, Koifman S. Head injury and brain tumours in adults: a case-control study in Rio de Janeiro. *Brazil Eur J Cancer Oxf Engl.* 2006;42:917–21.
27. Burch JD, Craib KJ, Choi BC, Miller AB, Risch HA, Howe GR. An exploratory case-control study of brain tumors in adults. *J Natl Cancer Inst.* 1987;78:601–9.
28. Carpenter AV, Flanders WD, Frome EL, Cole P, Fry SA. Brain cancer and nonoccupational risk factors: a case-control study among workers at two nuclear facilities. *Am J Public Health.* 1987;77:1180–2.
29. Zampieri P, Meneghini F, Grigoletto F, et al. Risk factors for cerebral glioma in adults: a case-control study in an Italian population. *J Neurooncol.* 1994;19:61–7.
30. Preston-Martin S, Mack W, Henderson BE. Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer Res.* 1989;49:6137–43.
31. Ryan P, Lee MW, North B, McMichael AJ. Risk factors for tumors of the brain and meninges: results from the Adelaide Adult Brain Tumor Study. *Int J Cancer.* 1992;51:20–7.
32. Schlehofer B, Blettner M, Becker N, Martinsohn C, Wahrendorf J. Medical risk factors and the development of brain tumors. *Cancer.* 1992;69:2541–7.
33. Annegers JF, Laws ER, Kurland LT, Grabow JD. Head trauma and subsequent brain tumors. *Neurosurgery.* 1979;4:203–6.
34. Inskip PD, Mellekjaer L, Gridley G, Olsen JH. Incidence of intracranial tumors following hospitalization for head injuries (Denmark). *Cancer Causes Control.* 1998;9:109–16.
35. Nygren C, Adami J, Ye W, et al. Primary brain tumors following traumatic brain injury—a population-based cohort study in Sweden. *Cancer Causes Control.* 2001;12:733–7.
36. Munch TN, Gørtz S, Wohlfahrt J, Melbye M. The long-term risk of malignant astrocytic tumors after structural brain injury—a nationwide cohort study. *Neuro-Oncol.* 2015;17:718–24.
37. Hochberg F, Toniolo P, Cole P. Head trauma and seizures as risk factors of glioblastoma. *Neurology.* 1984;34:1511–4.
38. Hu J, Johnson KC, Mao Y, et al. Risk factors for glioma in adults: a case-control study in northeast China. *Cancer Detect Prev.* 1998;22:100–8.
39. Chen Y-H, Keller JJ, Kang J-H, Lin H-C. Association between traumatic brain injury and the subsequent risk of brain cancer. *J Neurotrauma.* 2012;29:1328–33.
40. Howe GR, Burch JD, Chiarelli AM, Risch HA, Choi BC. An exploratory case-control study of brain tumors in children. *Cancer Res.* 1989;49:4349–52.
41. Kuijten RR, Bunin GR, Nass CC, Meadows AT. Gestational and familial risk factors for childhood astrocytoma: results of a case-control study. *Cancer Res.* 1990;50:2608–12.
42. McCredie M, Maisonneuve P, Boyle P. Perinatal and early postnatal risk factors for malignant brain tumours in New South Wales children. *Int J Cancer.* 1994;56:11–5.
43. Bunin GR, Buckley JD, Boesel CP, Rorke LB, Meadows AT. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the Children's Cancer Group. *Cancer Epidemiol Biomarkers Prev.* 1994;3:197–204.
44. Gurney JG, Preston-Martin S, McDaniel AM, Mueller BA, Holly EA. Head injury as a risk factor for brain tumors in children: results from a multicenter case-control study. *Epidemiology.* 1996;7:485–9.
45. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic brain injury: an overview of epidemiology, pathophysiology, and medical management. *Med Clin North Am.* 2020;104:213–38.
46. Bigler ED. Anterior and middle cranial fossa in traumatic brain injury: relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. *Neuropsychology.* 2007;21:515–31.
47. McKee AC, Stein TD, Kiernan PT, Alvarez VE. The neuropathology of chronic traumatic encephalopathy. *Brain Pathol.* 2015;25:350–64.
48. Cushing H. Meningiomas. In: Their classification, regional behaviour, life history, and surgical end results. Springfield: Thomas; 1938, p. 785.