

## Original Article

**Traumatic brain injury and subsequent glioblastoma development: Review of the literature and case reports**

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**Abstract**

**Background:** Previous reports have proposed an association between traumatic brain injury (TBI) and subsequent glioblastoma (GBM) formation.

**Methods:** We used literature searches and radiographic evidence from two patients to assess the possibility of a link between TBI and GBM.

**Results:** Epidemiological studies are equivocal on a possible link between brain trauma and increased risk of malignant glioma formation. We present two case reports of patients with GBM arising at the site of prior brain injury.

**Conclusion:** The hypothesis that TBI may predispose to gliomagenesis is disputed by several large-scale epidemiological studies, but supported by some. Radiographic evidence from two cases presented here suggest that GBM formed at the site of brain injury. We propose a putative pathogenesis model that connects post-traumatic inflammation, stem and progenitor cell transformation, and gliomagenesis.

**Key Words:** Brain tumor, glioblastoma, traumatic brain injury

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**Quick Response Code:****INTRODUCTION**

Glioblastoma (GBM) is the most common and deadly brain malignancy, with over 10000 new cases in the US annually and a median survival of only 14–16 months after surgical resection and concurrent chemoradiotherapy.<sup>[18,21]</sup> Molecular analysis of GBM biospecimens has led to the identification of specific driver mutations, which have formed the basis for subtyping GBM into the following groups: Proneural, neural, classical, and mesenchymal.<sup>[8,6,41,49]</sup> In a minority of cases, glioma or GBM arises in the context of specific genetic conditions caused by germline mutations in tumor

suppressor genes, namely, neurofibromatosis 1 (*NF1*), tuberous sclerosis (*TSC*), and Li-Fraumeni syndrome (*TP53*).<sup>[39]</sup> A rare genetic condition called Ollier disease,

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which is caused by mosaicism for a gain-of-function mutation in the gene encoding isocitrate dehydrogenase (*IDH1*), increases the risk for glioma formation, along with enchondromas.<sup>[2,40]</sup> Family history has also been linked to increased risk for GBM. Recent genome-wide association studies (GWAS), have pointed out single nucleotide polymorphisms (SNPs) that confer increased predisposition to developing glioma.<sup>[43,46,47,51,53,55]</sup> A notable such SNP is located on chromosome 8q24.21, within the locus of a long non-coding RNA (lncRNA) named *CCDC26*, which increases glioma risk approximately five times.<sup>[43,46,47]</sup> However, the role of predisposing genetic and environmental factors in gliomagenesis is still not well defined.

Environmental risk factors for GBM remain poorly defined, with the exception of exposure to ionizing radiation.<sup>[39]</sup> Here, we discuss a less known putative risk factor for gliomagenesis, traumatic brain injury (TBI).<sup>[3,14,56]</sup> In rare instances, formation of GBM has been documented in brain areas that were previously affected by injury. In the limited literature describing the association between TBI and GBM, the following criteria have been established which are suggestive of a causal relationship (reviewed in<sup>[56]</sup>):

1. The injury must be severe enough to cause a tissue repair process to commence;
2. The area of the traumatic injury should correspond directly with the location of the subsequent GBM;
3. There should be a gap of at least 1 year between the injury to the brain and the appearance of the tumor. A longer latent period is considered to be a stronger evidence of a causal relationship.

Here, we present two patients who developed GBM at the exact same site where they had suffered TBI several years ago. We also review relevant epidemiological studies, which are overall equivocal on the association between TBI and GBM. Finally, we propose a mechanism that could explain the biological link between TBI and gliomagenesis by invoking inflammation as the trigger for oncogenic transformation of neural stem and progenitor cells that migrate to the injured tissue for repair. Chronic inflammation has been shown to be a major predisposing factor for many solid tumors, including, but not limited to, hepatocellular carcinoma and colon cancer.<sup>[12]</sup> However, such a link has not been explored in gliomagenesis because of distinct immune properties of the brain. We postulate that, in a subset of patients, post-traumatic inflammation in the brain may predispose neural cells toward oncogenic transformation and glioma initiation.

## MATERIALS AND METHODS

We performed literature searches on PubMed to identify epidemiological studies that investigated the link between brain injury and GBM formation. We also collected and analyzed clinical and radiographic data from two patients with a history of TBI, who subsequently developed GBM.

## RESULTS

### Epidemiological studies

Several epidemiological studies have attempted to analyze the association between GBM formation and the presence of previous TBI. These studies present varying results regarding the strength of correlation and odds ratio for TBI-induced GBM. Nygren *et al.* performed a population-based cohort study in Sweden, which analyzed over 300,000 patients who were documented to have suffered traumatic brain injury between 1965 and 1994.<sup>[38]</sup> Overall, 400 cases of brain tumors were found. One fourth of these cases were excluded because they occurred within the first year after the TBI. This large study found no significant increase in the risk of brain tumor formation after TBI.<sup>[38]</sup> A similar cohort in Denmark showed a slightly elevated risk of brain tumor development following TBI,<sup>[23]</sup> even though the study was limited by a short follow-up time. A recent analysis of a very large cohort of over 400,000 patients in Denmark found no association between brain injury and risk of malignant glioma during the first 4 years after injury.<sup>[36]</sup> Interestingly, the same study found that brain injury was associated with long-term protection from malignant gliomas.<sup>[36]</sup>

A Taiwanese group analyzed a cohort of 5007 patients who visited ambulatory care centers between 2001 and 2002.<sup>[11]</sup> This study found that the incidence rate of malignant brain tumors was 6.28 per 10000 person-years in patients who had previously suffered TBI, compared to an incidence rate of 1.25 per 10000 person-years in control subjects. The odds ratio of developing an intracranial malignancy within 3 years of TBI was found to be 4.67 times greater for patients with TBI compared to those without. The authors also reported a statistically significant association between TBI severity and brain tumor development.<sup>[11]</sup>

Gurney *et al.* performed a multicenter case-control study in which the association between brain injury and tumor formation was analyzed specifically in children.<sup>[20]</sup> In a group of 801 children, the odds ratio for developing a primary brain tumor given previous TBI was found to be 1.4. Corrections for age, gender, and study site did not change the odds ratio. However, it was noted that certain variables within subgroups were associated with a significantly higher odds ratio. For example, children who had a birth injury and a subsequent head injury had an odds ratio of 2.6, whereas children with a forceps delivery and subsequent TBI had an odds ratio of 2.1. This finding may imply that multiple brain injuries (a brain injury in infancy followed by another TBI later in life) may be much more likely to produce a primary tumor than a single injury. The odds ratio for children who lost consciousness was increased to 1.6 compared to 1.4 for

the overall study. This increased odds ratio may indicate that the severity of the injury may correlate to the risk of developing a tumor. We hypothesize that this correlation may be due to the fact that more severe injuries may induce more inflammation.

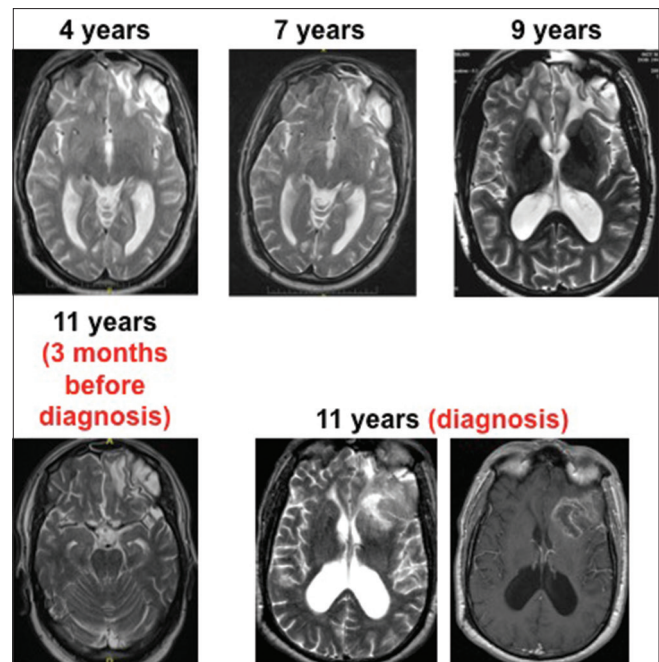
A study done by Preston-Martin *et al.*<sup>[42]</sup> found that head injury resulting in loss of consciousness or a permanent scar had an odds ratio of 1.9, which may lend some credence to the connection between brain injury severity and subsequent tumor development. Monteiro *et al.* found that patients with TBI had increased propensity for developing brain tumors (OR = 1.49).<sup>[34]</sup> This study also found that having two or more brain injuries resulted in an even higher odds ratio (3.14; adjusted for age, gender, and schooling), supporting the connection between severity and frequency of injury and subsequent tumor formation.

## CASE REPORTS

### Patient 1

This patient is a 65-year-old left-handed man, who suffered serious head trauma causing a large left frontal contusion at age 54 after a fall at the workplace. At that time, he was placed in a medically induced coma for 3 days. Serial imaging after the injury demonstrated encephalomalacia and gliosis at the site of the contusion [Figure 1]. He developed seizures 7 months after the injury. His seizures were well-controlled on lamotrigine until 11 years later when their frequency and severity increased. Imaging at that time remained unchanged. Three months later, he developed status epilepticus. Magnetic resonance imaging (MRI) of the brain revealed a large 4 cm heterogeneously enhancing tumor with a necrotic center in the left frontal lobe [Figure 1]. The tumor was in the same location as the original injury. Of note, it had been a mere 3 months since his last serial MRI, which showed no evidence of tumor.

In preparation for resection of the tumor, a Wada Test revealed bilateral hemispheric language dominance. To avoid damaging language-processing centers, awake language mapping was attempted during planned operative resection. The patient became agitated during language mapping and the surgeon opted to place subdural grid electrodes for extraoperative speech mapping, which revealed no regions associated with language function in the vicinity of the tumor. In a second operative procedure under general anesthesia, he underwent uneventful resection of >90% of the tumor with residual in the left insula. Histopathologic analysis confirmed the diagnosis of GBM. The Ki-67 immunolabeling index using MIB1 antibody was up to 25%. Immunohistochemistry for the R132H mutation in IDH1 was negative.



**Figure 1: Patient 1. Serial magnetic resonance images demonstrate that the glioblastoma arises at the site of encephalomalacia resulting from the brain injury to the left frontal lobe. All images are T2 sequences, except the last one, which is T1 postgadolinium**

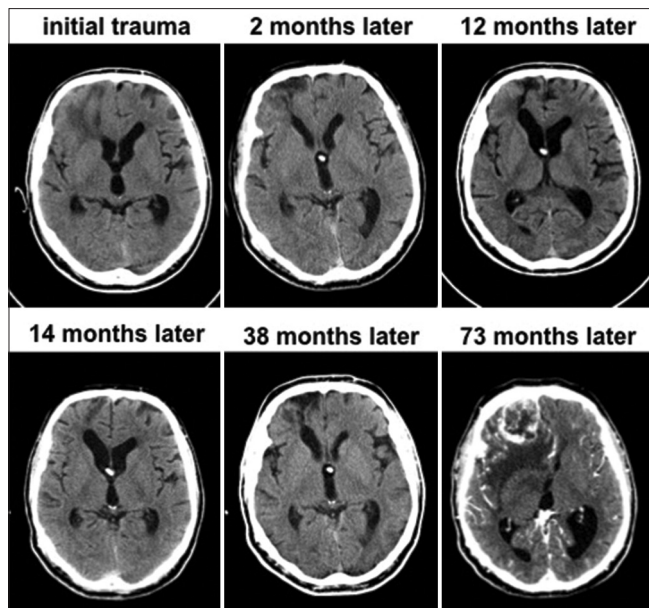
After surgery, he was treated with concurrent chemoradiotherapy (Stupp protocol). However, the tumor recurred rapidly and he expired within 4 months after surgery.

### Patient 2

This patient is a 54-year-old right-handed man who suffered a large contusion and severe injury to the inferior right frontal lobe in an automobile accident at age 47 [Figure 2]. Shortly after the injury, he developed post-traumatic hydrocephalus that was treated with a right frontal ventriculoperitoneal shunt. Subsequently, he required placement of a cardiac pacemaker that precluded imaging with MRI. He was followed with serial computed tomography (CT), which showed resolution of the contusion and development of encephalomalacia at the site of the inferior right frontal injury.

Seven years after the injury, he came again to medical attention due to headaches and confusion. CT imaging indicated a 4 cm heterogeneously enhancing inferior right frontal mass at the site of the brain injury. There was extensive vasogenic edema surrounding the lesion. He underwent right frontal craniotomy for gross total resection of the mass, which was diagnosed as GBM. Immunohistochemistry for the R132H mutation in IDH1 was negative. He was subsequently treated with chemoradiotherapy as per Stupp protocol. As per the most recent follow-up 8 months post-resection, he remains neurologically intact with no evidence for recurrence on CT.





**Figure 2: Patient 2.** Serial computed tomography scans spanning a 73-month period show that the glioblastoma in the inferior right frontal lobe developed at the site of the contusion. All images are without contrast, except the last one

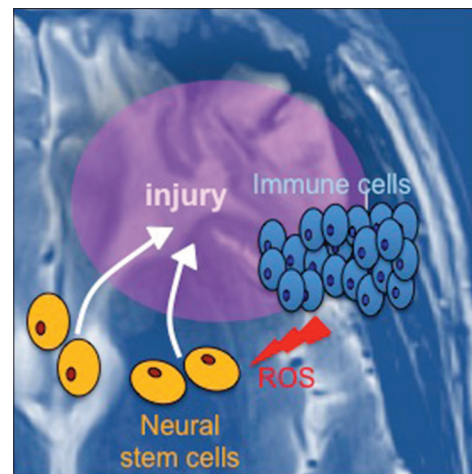
## DISCUSSION

Epidemiological studies are largely equivocal on the link between TBI and subsequent formation of malignant glioma. In fact, large-scale studies have shown no correlation. However, the two presented cases show GBM formation at the site of prior brain injury. Our hypothesis is that, in some patients, an underlying biological vulnerability predisposes them to gliomagenesis after brain trauma. What are the mechanisms that could potentially explain injury-driven gliomagenesis?

We propose that the inflammatory response that ensues after TBI is linked to oncogenic transformation of neural stem and progenitor cells that chemotactically migrate to the injured site in response to inflammation [Figure 3]. The link between injury, inflammation, and cancer has been firmly established in other organ systems. For example, the robust inflammatory response associated with hepatitis and pancreatitis is a grave risk factor for the development of hepatocellular carcinoma and pancreatic cancer, respectively.<sup>[12]</sup> It is, therefore, plausible that similar processes may underlie injury-driven gliomagenesis in the brain.

### Inflammation

Inflammation at the site of brain injury is well-documented in the literature.<sup>[25,29,32,37,52]</sup> In the acute post-trauma period, there is sequential mobilization of resident brain microglia and myeloid inflammatory cells to the site of injury. Peripheral neutrophils, monocytes, and eosinophils are recruited to the site within hours and can remain for extended periods of time.<sup>[25]</sup> These



**Figure 3: Model linking traumatic brain injury to glioblastoma formation.** Upon injury to the brain, neural stem cells migrate to the site to enable tissue repair. At the same time, immune cells are recruited. Immune cells release reactive oxygen species (ROS), which can induce mutagenesis and initiate oncogenic transformation of stem cells

inflammatory cells can contribute to oncogenesis via the generation of reactive oxygen species (ROS), which have mutagenic properties, or via secretion of growth factors and cytokines that have mitogenic effects on neural stem and progenitor cells, in addition to prolonging the inflammatory response.<sup>[29,32,37]</sup> For example, eosinophils have been linked to the initiation and progression of GBM.<sup>[13]</sup> Eosinophilic granular contents have been shown to cause significant damage to tissues in an effect known as the Gordon phenomenon.<sup>[13,16]</sup> Eosinophil-derived neurotoxin (EDN), eosinophil cationic protein, and eosinophil protein X (EPX) have been experimentally shown to produce cellular damage in neural tissues during degranulation.<sup>[16]</sup> In addition, eosinophil peroxidases generate ROS, which may lead to mutagenesis.<sup>[12,13,35]</sup>

A number of inflammatory cytokines, including IL-1, TNF, IL-10, IL-6, IL-8, and MCP-1, are known to be upregulated in the context of TBI and facilitate recruitment of myeloid immune cells.<sup>[37]</sup> Furthermore, studies have provided evidence that single nucleotide polymorphisms (SNPs) in interleukin-4 receptor alpha (IL-4R $\alpha$ ) and interleukin-13 (IL-13) may be risk factors in GBM formation.<sup>[45]</sup> Cytokines IL-4 and IL-13 both activate the IL-4R $\alpha$  receptor on cells of the immune system, leading to similar downstream responses, which ultimately result in the release of chemoattractants, such as eotaxin and MCP-1. These chemokines result in the migration of eosinophils and monocytes into the area of damage.<sup>[27,37]</sup>

### Stem cell migration to injury site

Neural stem cells in the adult brain localize primarily to two neurogenic areas, namely, the subventricular

zone of the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus (for review see<sup>[33]</sup>). There is also speculation that neural stem or progenitor cells may reside in cortical areas, however, this is debatable.<sup>[44]</sup> Neural stem cells in neurogenic niches generate lineages that populate the brain: Neurons, astrocytes, and oligodendrocytes. Neural stem cells and descendant progenitor cells chemotactically migrate to the sites of brain injury and participate in the repair and recovery.<sup>[15,19,24,48,54]</sup> Ependymal cells, which line the inner walls of the ventricles, may also proliferate and differentiate into neuroblasts and astrocytes following trauma in mice and humans.<sup>[4,9]</sup> Such chemoattraction-mediated migration has been demonstrated in the case of various injury-generating insults, namely, ischemia, demyelination, and, importantly for our purposes, physical trauma.<sup>[15]</sup> GBM may, therefore, result from transformation of neural stem or progenitor cells as they migrate to the injury to repair tissue damage.

The oncogenic potential of neural stem cells has been suggested by the observation that neurogenic niches in the brain are sensitive to chemical oncogenesis.<sup>[22,44,50]</sup> Experimental models involving overexpression of oncogenes and inactivation of tumor suppressor genes in neural stem cells suggest that they can generate GBM tumors (reviewed in<sup>[33]</sup>). The fact that GBM tumors are frequently found in the periventricular zone or in direct contact with the subventricular zone supports this hypothesis.<sup>[1,5,10,26]</sup> Genetic models in mice have raised the possibility that oligodendrocyte progenitors may also represent a putative cell-of-origin in GBM.<sup>[30]</sup> Other studies have suggested that even terminally differentiated brain cells, such as neurons and astrocytes, can give rise to GBM by undergoing dedifferentiation driven by genetic alterations.<sup>[17,31]</sup> In addition, astrocytes near a stab wound proliferate within their lineage *in vivo*, however, a fraction of astrocytes from injured brain tissue demonstrates long-term stem cell-like activity in an *in vitro* neurosphere assay, suggesting the possibility of a return to multipotency under certain conditions.<sup>[7,28]</sup> Collectively, these observations suggest that several neural cell types that migrate to TBI sites are capable of undergoing oncogenic transformation.

## CONCLUSION

In conclusion, large-scale epidemiological studies have not shown a definitive link between TBI and increased risk of developing GBM. However, the two patients presented here developed GBM at the site of their brain injury several years later. It is, therefore, possible that an underlying biological vulnerability in a subset of patients with TBI may predispose them to gliomagenesis. We propose a putative model that links neuroinflammation to mutagenesis in neural stem and progenitor cells

migrating to the site of injury, leading to their neoplastic transformation and glioma initiation. In the future, as molecular mechanisms of gliomagenesis and the brain's response to TBI become clearer, we hope to identify the biological mechanisms that make a subset of patients susceptible to brain tumor formation after injury.

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## Conflicts of interest

There are no conflicts of interest.

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