

Traumatic glioblastoma: commentary and suggested mechanism

Journal of International Medical Research

2018, Vol. 46(6) 2170–2176

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DOI: 10.1177/0300060518771265

journals.sagepub.com/home/imr

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Abstract

The role of head trauma in the development of glioblastoma is highly controversial and has been minimized since first put forward. This is not unexpected because skull injuries are overwhelmingly more common than glioblastoma. This paper presents a commentary based on the contributions of James Ewing, who established a major set of criteria for the recognition of an official relationship between trauma and cancer. Ewing's criteria were very stringent. The scholars who succeeded Ewing have facilitated the characterization of traumatic brain injuries since the introduction of computed tomography and magnetic resonance imaging. Discussions of the various criteria that have since developed are now being conducted, and those of an unnecessarily limiting nature are being highlighted. Three transcription factors associated with traumatic brain injury have been identified: p53, hypoxia-inducible factor-1 α , and c-MYC. A role for these three transcription factors in the relationship between traumatic brain injury and glioblastoma is suggested; this role may support a cause-and-effect link with the subsequent development of glioblastoma.

Keywords

Traumatic cancer, traumatic brain injury, glioma, glioblastoma, transcription factors, Ewing's criteria

Date received: 31 January 2018; accepted: 26 March 2018

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Introduction

This paper presents a commentary on the major criteria established for the association between trauma and cancer, more specifically between traumatic brain injury (TBI) and gliomas. Particular focus is placed on glioblastoma, which is the most frequent as well as the most lethal type of glioma.

The criteria discussed herein were assessed for their feasibility at the clinical, surgical, and histopathologic levels. An attempt was made to determine the degree to which they were meant to solve the formidable issue of the disproportion between traumatic events, including those affecting the skull, and the subsequent occurrence of cancer. Furthermore, a possible molecular mechanism linking trauma and cancer is herein proposed.

Criteria associating trauma with cancer

Although not the first to have addressed the issue, James Ewing¹ defined five criteria in 1935 that should limit the relationship between a traumatic injury and the subsequent development of a malignant tumor. By "limit," Ewing meant that traumatic incidents are much more frequent than a possibly related tumor. Moreover, this scholar believed that a neoplasm will develop rarely in this context, if at all. Ewing proposed that in only a tiny minority of cases, perhaps in none whatsoever, will the patient receive compensation following recognition of the tumor as a traumatic-induced cancer.¹

Ewing's first criterion

First, Ewing stated the following: "The injury should be authenticated." When a compensation complaint is addressed to the court of law, some magistrates might

accept the facts presented by the plaintiff at their face value, while forensic pathologists will be more scientific in their approach. Thus, they should recognize chronic irritation and occupational hazards as distinct from an injury that leads to a traumatic tumor.¹ However, is this indeed feasible?

Ewing's second criterion

Second, Ewing stated, "The preserved nature of the tissues prior to the injury should be proven."¹ However, how often is an individual thoroughly examined while expecting to sustain head trauma? In our opinion, this criterion is very weak. How frequently is a subclinical tumor discovered through a traumatic blow that has been directed at it? Is traumatic determinism indeed reality or fiction?

Ewing's third criterion

Ewing's third criterion is as follows: "The neoplasm should develop at the very site of the previous trauma."¹ However, in patients with coup and contrecoup head injuries, the above sequence might not precisely occur because the lesion of the injury is located at the opposite pole of the skull. In patients who fall from a height, total body trauma will occur. But where is the tumor expected to develop?

Ewing's fourth criterion

The fourth criterion is as follows: "A minimal lapse of time should separate the trauma from the appearance of the subsequent tumor." The delay may be years, as for a carcinoma (up to 20 years); alternatively, it may be as brief as 3 to 5 weeks, as for a sarcoma. Ewing believed that such periods of latency will allow further damage to occur, which may sustain the malignant transformation. Conversely, an absence of a delay will support a cancer that had been incipient before the injury.¹

Ewing's fifth criterion

Finally, Ewing stated, "A positive diagnosis (not established by exception) will confirm the presence and the type of the cancer." In the case of a smoldering tumor, the diagnosis may help to exclude a traumatic cancer. Ewing further implied that a traumatic tumor will carry histologic traits of the injury, including persistent and exuberant repair;¹ however, these traits may be difficult to apprehend.

Among the various types of tumors that might be associated with trauma, Ewing examined gliomas.

Ewing and traumatic gliomas and glioblastomas

Ewing summarized his long-term interest in this issue as follows¹:

"Adler collected 1086 cases of glioma of the brain, of which 8.8 percent were preceded by a rather definite history of trauma. The critical study of Parker and Kernohan showed that of 491 cases of glioma of the brain 4.8 per cent could be considered as possibly of traumatic origin, although 13.4 per cent gave a history of previous skull injury. Yet in an equal number of other patients 10.4 per cent gave a history of severe skull injury and of 200 normal persons 35.5 per cent gave a history of skull injury. They also followed 2858 war injuries of the skull for 14 years without finding a single brain tumor. Vogeler, Ackerman and others report 2775 cases of skull injuries followed for many years, finding a great variety of neurological sequels but no tumors."

"One of the most significant features of this debate is the fact that in one of Beneke's cases, an experienced observer accepted without question the statements of the claimant which strongly favored a

traumatic origin of the tumor, but that when the actual clinical facts were secured, a history of severe cerebral attacks before the accident was established and the traumatic origin was clearly excluded."

To summarize this brief overview, Ewing concluded that a thorough analysis of all of these data should lead to the conclusion that nearly no traumatic tumor should be confirmed as such. Ewing further implied that the systematic recognition of glioblastoma as a traumatic tumor by prompting widespread compensation might severely compromise modern countries' financial establishments.¹ However, by systematically rejecting the possibility that even a small proportion of cases are in fact traumatic glioblastomas, one might cancel out the maxim: "En médecine comme en amour, il n'y a ni jamais ni toujours" (i.e., "In medicine as in love, there is neither never nor always").

Considering the present knowledge on carcinogenesis, the possibility that TBI is one of multiple factors involved in the pathogenesis of glioblastoma cannot be completely excluded. Skull trauma may even be the initiating factor in the malignant transformation. If confirmed, the compensatory institutions might have to reevaluate their intervention protocols.

Ewing's successors

In 1974, Zulch et al.² revised Ewing's criteria while adding their own input. Ewing's second criterion became Zulch's first criterion: "The patient was in good health before the accident." However, this criterion remains strictly subjective.

Zulch's second criterion is: "The injury should cause at least a contusion or a scar." Such lesions may also be caused, to some extent, by mild trauma. This is the first quantification of the injury in this context, but its significance is not completely clear.

In Zulch's third criterion, Ewing's third and fifth criteria are associated: "The tumor should develop in continuity with the blow."

Zulch's fourth criterion is the same as Ewing's fourth criterion. In a somewhat arbitrary manner, the authors state that the latent period should be ≥ 1 year; however, this precise timing may not rest on very firm grounds.

Zulch's fifth criterion is similar to Ewing's fifth criterion.

Finally, Zulch's sixth criterion is clear and acceptable²: "The trauma should be exogenous."

In 1978, Manuelidis³ added three histopathology-based criteria:

1. "The trauma should be histologically confirmed." This criterion lacks practicality because the surgeon will seldom be distracted from his or her main goal, which is excision of the glioblastoma.
2. "Bleeding, edema, and scars should be distinguished from TBI." However, this criterion is difficult to confirm histologically.
3. "The tumor should be in direct continuity with the traumatic scar."³ However, this feature cannot be based on histology alone.

In 2004, Moorthy and Rajshekhar⁴ added their own imaging-based criteria:

1. "CT/MRI will confirm evidence of the traumatic contusion," which is a very timely and practical adjunct.
2. "CT/MRI will assess the evidence of the tumor being adjacent to the contusion." This is even more supportive than histologic findings.
3. A new criterion: "Contrast CT/MRI, performed shortly after the resorption of the traumatic contusion, should not disclose any mass lesion." Notably, contrast brain MRI is rarely used today.

The timely progress in imaging is especially welcome in relation to our inquiry.

A suggested mechanism for TBI

Xiong et al.⁵ proposed that TBI may modify the brain energy metabolism by disturbing the transduction process and calcium transport at the mitochondrial level. Therefore, it seems that the induction of oxidative stress and the disruption of cellular calcium homeostasis have major roles in TBI.⁵ A recent study showed that glioblastoma acquires metabolic reprogramming.⁶ In that study, the voltage-dependent anion channel 1 (VDAC1), a mitochondrial protein that controls cell energy and metabolic homeostasis, could be silenced to reverse the reprogrammed metabolism, thus inducing differentiation and loss of the invasive capacity.⁶

The authors also reported that VDAC1 depletion modified transcription factor profiles.⁶ Mostly affected were the expression levels of the major transcription factors p53, hypoxia-inducible factor-1 α (HIF-1 α), and c-MYC, which are also known to regulate the metabolism, growth, proliferation, and differentiation of cells. VDAC1 depletion induced an increase in p53 expression and a reduction in HIF-1 α and c-MYC expression while leading to normalization of malignant parameters such as cell proliferation, loss of differentiation, and aerobic glycolysis.⁶

These transcription factors are known to modulate the expression of several molecules, including those sustaining glycolytic metabolism. Therefore, we cannot exclude the possibility that regulation of the above three transcription factors, as well as of VDAC1, may be involved in both TBI and metabolic reprogramming (including aerobic glycolysis; i.e., the Warburg effect). These four factors should be investigated as agents of a possible link between TBI and glioblastoma carcinogenesis.⁷⁻⁹

p53 induces neuronal apoptosis and initiates regeneration after TBI, perhaps

by means of activation of the p53-induced death domain protein.⁸

Inflammation, which is necessary to heal wounds and maintain tissue homeostasis, may in fact be associated with all phases of tumor development. Being a cellular stressor, however, inflammation may also induce DNA damage and genetic instability. Chronic inflammation may cause malignant transformation through mutations or epigenetic pathways. Among the activated oncogenes, c-MYC plays a major role in both inflammation and malignant transformation. Its transcription program is dependent on the cellular context and may vary from increased proliferation to activated apoptosis. The c-MYC gene is often deregulated by inflammation. Endogenous c-MYC is critical for efficient induction of p53-dependent apoptosis following DNA damage.¹⁰

c-MYC expression as demonstrated by immunohistochemical examination of rat brains has suggested that c-MYC expression may be a marker of brain trauma.⁷

HIF-1 α regulates several adaptive responses to hypoxia, one of which has been proposed for use in the regenerative treatment of TBI.⁹ This transcription factor has also been used to treat brain edema and disruption of the blood-brain barrier in patients with TBI.¹¹ The Warburg effect and HIF-1 α activation in inflammatory reactions may be associated with each other after head trauma has occurred. Therefore, by extrapolation, common pathways may exist between inflammation and cancer.¹²⁻¹⁴

The association between trauma and inflammation is more readily identified in non-brain tumors, especially those of body surfaces such as the skin or gastrointestinal tract. The inflammation that develops after acute injury may be acute^{15,16} and involve an oxidative burst and neutrophil production. However, this phase is transient; it is usually the chronic inflammatory stage, together with the repair process, if altered,

that will increase the probability of malignant transformation.¹⁶

Xiong et al.⁵ examined TBI in animal models and observed oxidative stress and disruption of cellular calcium homeostasis, but no brain cancer. Arif et al.⁶ investigated glioblastoma and its relationship with c-Myc, HIF-1 α , and p53 as well as with FOXO3, STAT3, and AP2. They also investigated other transcription factors that regulate the transformed phenotype.¹⁷⁻²²

Discussion

We have commented on the main criteria, or at least the most well known criteria, that correlate trauma with the consequent development of a malignant tumor. Most of the data indicate that the association is weak. Some scholars, such as Ewing,¹ profess that such an association is almost nonexistent.

The criteria were carefully scrutinized in the present commentary, and any evidence of bias was highlighted. The total absence of a relationship between trauma and cancer, most specifically between TBI and glioblastoma, is not acceptable. This is because TBI initiates inflammation, repair, oncogene activation, and metabolic reprogramming and should therefore lead to malignancy in at least some cases.^{15,16}

Moreover, we have underlined several occurrences in which the three transcription factors p53, HIF-1 α , and c-MYC have served as a link between TBI with its inflammatory and repair consequences and the development of brain cancer.⁷⁻⁹

Injury and inflammation have been associated with skin cancers in the context of burns or other recurrent trauma. However, their combined involvement in the initiation of glioblastoma, especially as reflected by epidemiologic studies, is far from confirmed. Together with HIF-1 α , the c-Myc oncogene plays a role in inflammation. Therefore, we hypothesize that these transcription factors together with

inflammation have a function in the development of glioblastomas after TBI. Trauma-associated gliomagenesis may be explained by TBI-induced inflammation, in turn leading to malignant transformation of neighboring neural progenitor cells.²³

Animal models, mainly rats, have been used for TBI investigations.^{5–9,11,13,14,16} The above-mentioned experimental markers have been evoked in animal models of glioblastoma,⁶ to our knowledge, however, no brain cancers were initiated by skull trauma in these laboratory animals. In fact, the eventuality of brain tumor development in rats subjected to head trauma is remote because of the long “incubation” period (lag) needed.

An enhanced correlation between traumatic injury and cancer, notably with glioblastoma, is suggested by the above molecular findings. This correlation may justify our impression that the herein-discussed criteria are indeed more rigid than necessary.

Conclusion

The association between head trauma and glioblastoma, as suggested above, should be confirmed by additional experimental data regarding the modulation of the above-mentioned transcription factors described in TBI. Objective molecular criteria regarding the above correlation as well as a scheme for future treatment implications will sustain the diagnostic and therapeutic facets of traumatic glioblastoma. In addition, the molecular data presented in this review are inconsistent with the stringent nature of the consensus criteria.

Acknowledgment

We thank Kibbutz Sde-Boker for providing support.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

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

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