ORIGINAL ARTICLE

Is Concussion a Risk Factor for Epilepsy?

Richard Wennberg, Carmen Hiploylee, Peter Tai, Charles H. Tator

ABSTRACT: *Background:* Epidemiologic studies have suggested that concussion, or mild traumatic brain injury (mTBI), is associated with a twofold or greater increase in relative risk for the development of post-traumatic epilepsy. To assess the clinical validity of these findings, we analyzed the incidence of epilepsy in a large cohort of post-concussion patients in whom concussion was strictly defined according to international guidelines. *Methods:* A retrospective cohort study of 330 consecutive post-concussion patients followed by a single concussion specialist. Exclusion criteria: abnormal brain CT/MRI, Glasgow Coma Scale < 13 more than 1-hour post-injury, hospitalization >48 hours. Independent variable: concussion. Outcome measure: epilepsy incidence (dependent variable). *Results:* The mean number of concussions/patient was 3.3 ($\pm$2.5), mean age at first clinic visit 28 years ($\pm$14.7), and mean follow-up after first concussion 7.6 years ($\pm$10.8). Eight patients were identified whose medical records included mention of seizures or convulsions or epilepsy. Upon review by an epileptologist none met criteria for a definite diagnosis of epilepsy: four had episodic symptoms incompatible with epileptic seizures (e.g., multifocal paraesthesiae, multimodality hallucinations, classic migraine) and normal EEG/MRI investigations; four had syncopal ($n = 2$) or concussive ($n = 2$) convulsions. Compared with annual incidence (0.5/1000 individuals) in the general population, there was no difference in this post-concussion cohort ($p = 0.49$). *Conclusion:* In this large cohort of post-concussion patients we found no increased incidence of epilepsy. For at least the first 5-10 years post-injury, concussion/mTBI should not be considered a significant risk factor for epilepsy. In patients with epilepsy and a past history of concussion, the epilepsy should not be presumed to be post-traumatic.

RÉSUMÉ: Les commotions cérébrales représentent-elles un facteur de risque pour l'épilepsie? *Contexte:* Des études épidémiologiques ont suggéré que les commotions cérébrales ou les traumatismes cranio-cérébraux (TCC) légers pouvaient être associés à une augmentation deux fois plus élevée (ou nettement plus grande) d'être atteint d'épilepsie post-traumatique. Afin d'examiner la validité clinique de ce constat, nous avons analysé l'incidence de l'épilepsie au sein d'une vaste cohorte de patients ayant souffert précédemment d'une commotion cérébrale et pour lesquels ce traumatisme a été identifié rigoureusement en vertu de lignes directrices internationales. *Méthodes:* Il s'est agi d'une étude de cohorte rétrospective rassemblant 330 patients successifs ayant souffert d'une commotion cérébrale. Tous ces patients avaient été suivis par le même spécialiste des commotions cérébrales. Des critères d'exclusion avaient été établis : présence d'anomalies cérébrales détectées par tomographie assistée par ordinateur et par IRM ; <13 obtenu à l'échelle de Glasgow, et ce, plus d'une heure à la suite du traumatisme ; hospitalisation >48 heures. Cette étude comportait une variable indépendante : les commotions cérébrales ; le résultat clinique, lui, cherchait à mesurer l'incidence de l'épilepsie (variable dépendante). *Résultats:* Le nombre moyen de commotions cérébrales par patient était de 3,3 ($\pm$ 2,5) ; leur âge moyen au moment de leur première consultation était de 28 ans ($\pm$ 14,7) ; enfin, la période de suivi moyen après la première commotion cérébrale était de 7,6 ans ($\pm$ 10,8). Huit patients préalablement identifiés possédaient des dossiers médicaux où il était question de convulsions, d'attaques convulsives ou d'épilepsie. Après qu'un épileptologue a analysé leurs dossiers, aucun patient ne satisfaisait aux critères autorisant un diagnostic précis d'épilepsie. Ainsi, quatre d'entre eux avaient montré des symptômes épisodiques ne correspondant pas à ceux des crises épileptiques (p.ex. : des signes de paresthésie multifocale, des hallucinations multimodales, des signes de migraine avec aura) et des résultats d'électroencéphalographie et d'IRM normaux. On a aussi détecté chez quatre autres patients des convulsions entraînant une perte de connaissance ($n = 2$) ou des convulsions apparues à la suite d'une commotion cérébrale ($n = 2$). Au sein de notre cohorte post-commotion cérébrale ($p = 0,49$), aucune différence n'a émergé par rapport à l'incidence annuelle au sein de la population générale (0,5/1000 individus). *Conclusions:* Nous n'avons pas observé d'augmentation de l'incidence de l'épilepsie au sein de cette vaste cohorte de patients ayant été victimes antérieurement d'une commotion cérébrale. Pour au moins les 5 à 10 premières années consécutives à une commotion cérébrale ou à un TCC léger, ces derniers ne devraient pas être considérés comme des facteurs de risque importants en ce qui a trait à l'épilepsie. Chez des patients ayant des antécédents d'épilepsie et de commotion cérébrale, on ne devrait pas présumer que l'épilepsie est d'origine post-traumatique.

INTRODUCTION

> "It has been asserted almost universally that trauma may cause epilepsy; I have never been able to understand why."
> A. Kinnier Wilson (1923)

The above quotation from a giant in clinical neurology appeared as an epigraph to Jennet's classic "Epilepsy after non-missile head

From the Canadian Concussion Centre, University Health Network, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada (RW, CH, CHT); Division of Neurology, University Health Network, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada (RW, PT); Division of Neurosurgery, University Health Network, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada (CHT).

Correspondence to: Richard Wennberg, Toronto Western Hospital, 399 Bathurst Street, Suite 5W444, Toronto, ON, Canada M5T 2S8. Email: richard.wennberg@uhn.ca

injuries."[1] Over the near half-century since the publication of Jennet's book, much has been learned about the epidemiology of traumatic brain injury (TBI) and the risk of post-traumatic epilepsy. Specifically, TBI is now accepted as the cause of 3%-9% of all epilepsy cases.[2-5] It is also accepted that the risk of post-traumatic epilepsy is highest after severe TBI with intracranial hemorrhage and/or prolonged (e.g., >24 hours) loss of consciousness, and less elevated after moderate TBI with loss of consciousness 0.5-24 hours and Glasgow Coma Scale (GCS) 9-12 more than an hour post-injury.[2,3,5-7] Furthermore, it has been shown that the risk for post-traumatic seizures and epilepsy is highest during the first few years post-injury and in people with a family history of epilepsy.[2,3,5,7,8]

Mild traumatic brain injury (mTBI), or concussion, is an order of magnitude more common than moderate and severe TBI, with an annual incidence of at least 2-6/1000 individuals.[9-12] It has been estimated that sports-related concussions alone affect more than a million people annually in North America,[10] and interest in the acute and chronic effects of concussions, especially as related to sports, has burgeoned over the past two decades.[13-16] Terminologically, mTBI and concussion are typically used interchangeably,[14,15] although discussants at the 5th International Conference on Concussion in Sport considered the possibility that concussion might represent a lesser degree of injury within the mTBI category, at the lowest end of a TBI spectrum from mild to severe.[15] Notwithstanding, there are no currently accepted criteria differentiating concussion from mTBI, and the two terms will thus be used synonymously in this paper to indicate a brain injury induced by biomechanical forces that "results in a range of clinical signs and symptoms that may or may not involve loss of consciousness," typically with a "rapid onset of short-lived impairment of neurological function that resolves spontaneously," and "no abnormality … on standard structural neuroimaging studies."[15] Post-concussion symptoms usually resolve within 10-14 days in adults, and within 1 month in children, but in a minority of cases there may be persistent sequelae lasting months or even years.[15,17] There is conflicting evidence as to whether post-traumatic epilepsy may be one of the sequelae of concussion/mTBI.

In the concussion literature, post-traumatic epilepsy has rarely been mentioned as a complication of concussion/mTBI.[16,18] However, in the epilepsy literature mTBI is reported to carry an approximately twofold increased risk for epilepsy, with a sixfold increased incidence in those with a family history of epilepsy.[3,5,7,19,20] Some studies reported the increased risk to persist more than 10 years after mTBI,[5,7,20] however, other studies found no increased risk beyond 5 years.[2,3,19] In the broader epilepsy community, despite the epidemiologic literature, there is evidence of uncertainty regarding the relation between concussion/mTBI and epilepsy. For example, the public information section of the Epilepsy Foundation website states: "Mild head injuries, such as a concussion with just a very brief loss of consciousness, do not cause epilepsy. Yet the effects of repeated mild head injuries and epilepsy is unknown."[21]

The existence of different perspectives in the concussion and epilepsy literature, discrepancies in the epidemiologic literature, and ambiguity in the epilepsy community regarding the clinical validity of the epidemiologic data raises the question of possible confounding issues. Four categories of potential confounds merit consideration at the introductory stage of any investigation into the risk of epilepsy after mTBI/concussion.

Accuracy of diagnosis and classification of head injury severity

One of the problems affecting the epidemiologic studies cited above is a lack of diagnostic accuracy regarding the severity of head injury in the populations studied. The studies of cases identified through the Medical Records Linkage System of the Rochester Epidemiology Project at the Mayo Clinic[2,3,19] included both hospitalized and non-hospitalized patients as well as clinical information on the circumstances and characteristics of the TBIs.[3] Those studies were more likely able to reliably separate mild and moderate and severe TBI cases than the studies based entirely on registry data sets using International Classification of Diseases (ICD) codes for TBI classification, obtained principally in hospitalized patients.[5,7] International Classification of Diseases codes are developed primarily for administrative purposes, and are not ideal for use in epidemiologic TBI studies,[8,12,22] particularly for classification of mTBI.[23,24] Another problem is that most patients with concussion/mTBI do not present to hospital and are thus not included in registry data sets limited to hospitalized patients.[5,7,12] The historical lack of a universal system for diagnosis and classification of TBI has also contributed to heterogeneity in TBI classification in previous studies.[12,25-27]

Accuracy of diagnosis of epilepsy and classification of seizures

As with the diagnosis and classification of TBI severity, the diagnosis of epilepsy from ICD codes in registry data sets[7] is prone to inaccuracy. However, this problem was avoided in some studies by methods that included detailed review of the medical records of identified cases.[2,3,5]

In the population studied by Jennet, early (within 7 days of injury) post-traumatic seizures increased the risk of late (beyond 7 days) post-traumatic epilepsy,[1] and a classification that separates early and late post-traumatic seizures persists to this day.[28-31] A subdivision of the early post-traumatic seizure category to include an "immediate" classification, as first suggested by Elvidge,[28,32] has been complicated by the existence of two different definitions: (a) a seizure occurring within 24 hours of injury,[28,30,31] or (b) a seizure occurring immediately after impact.[29] This discrepancy is a source of ongoing diagnostic confusion, and only the second definition—known as a concussive convulsion—describes an entity distinct from other early post-traumatic seizures.

Concussive convulsions or impact seizures

Jennet[1] recognized in his neurosurgical population the existence of a distinct form of seizure he called "immediate epilepsy," and which he described as the occurrence of a generalized convulsion "within moments of injury." He further described a benign natural history of such events in his patients: "This uncommon phenomenon consisted … exclusively of a generalised fit following a mild injury in an adult; none of the small number of such patients … had any further epilepsy."[1] Studies over the past 20 years, primarily based on video analysis of such events in elite athletes, have further refined the clinical description of the convulsions: onset within 2 seconds of impact, loss of consciousness and a brief tonic phase followed by myoclonic or clonic jerking of the extremities lasting <150 seconds; reported incidence is ~1/70 concussions.[33,34] There may occasionally be more subtle motor manifestations, particularly brief tonic posturing without subsequent clonic movements.[35] These events are now referred to as concussive convulsions or "impact seizures," and

they have been demonstrated to carry no risk for the later development of epilepsy.[33-36] They may occur in children as in adults,[36] and current practice recommendations advise against a need for neuro-imaging or electroencephalography (EEG) investigations.[34,36] Failure to accurately diagnose a concussive convulsion, and to consider it the same as an early post-traumatic seizure, has been demonstrated to have the potential for adverse consequences, given the very different natural histories of the distinct entities.[37]

In the sports concussion literature, concussive convulsions/impact seizures and their associated benign natural histories are well recognized and regularly included in consensus statements.[13,14] In contrast, concussive convulsions appear less well recognized in the general epilepsy literature, and have not been considered in population-based epidemiologic studies of epilepsy risk after TBI. The methods of the most recent population-based study would have excluded concussive convulsions by excluding all single seizures that occurred <7 days after a TBI,[5] however, concussive convulsions may have been included as incident cases of post-traumatic epilepsy in the other large population-based studies.[2,3,7,19]

Exacerbation of pre-existing epilepsy by mild head injury

Another potential confound for studies exploring the risk of epilepsy after mTBI is that a pre-existing epilepsy may be exacerbated, or revealed, by a concussion/mTBI. Formally described to occur in patients with focal and generalized epilepsies,[38] clinical experience suggests that the phenomenon may be most common in patients with primary (idiopathic) generalized epilepsy. The possibility that a mild head injury could reveal a hitherto latent primary generalized epilepsy, especially in a child or adolescent (given the childhood and adolescent onset of the typical primary generalized epilepsy syndromes), could be relevant to the sixfold increased risk of epilepsy after mTBI in children and young adults with a family history of epilepsy.[7,20] In other words, individuals with a primary generalized epilepsy syndrome may have had their condition revealed, or unmasked, by a concussion/mTBI, rather than caused by the head injury per se. It is of course impossible to know whether or not such a primary generalized epilepsy would have remained forever latent, or would have ultimately manifested spontaneously, but it would be imprecise to attribute the fundamental cause of the genetically predetermined epilepsy to the mTBI; that is, even if the initial clinical manifestation of the epilepsy was hastened by a preceding concussion, it would be incorrect to consider the concussion responsible for a *de novo* epilepsy.

Primary generalized epilepsies unmasked by mTBI would understandably be captured as post-traumatic epilepsy in epidemiologic studies; exacerbation of pre-existing epilepsy by mTBI was also potentially classifiable as incident post-traumatic epilepsy in the most recent population-based study, where epilepsy patients seizure-free off medications for 5 years before TBI were declared in remission.[5]

With the goal of further exploring the question of whether concussion is a risk factor for the development of *de novo* epilepsy, we had the opportunity to study the subject from a novel viewpoint, specifically through follow-up of a large cohort of post-concussion patients, all with a history of strictly defined concussion/mTBI. In this way, we were able to: (a) circumvent the heterogeneity of TBI classification present in previous population-based studies, and (b)

ensure diagnostic accuracy of post-traumatic epilepsy by recognizing cases of concussive convulsions or pre-existing epilepsy.

METHODS

This was a retrospective cohort study carried out in an academic tertiary care center (University Health Network [UHN], Toronto Western Hospital). Participants were 330 consecutive post-concussion patients (199 male, 131 female) followed by one concussion specialist (CHT) between 1997 and 2015. Concussion/mTBI was defined in accordance with the current consensus statements on concussion in sport.[14-16] The following exclusion criteria were employed to ensure accuracy of concussion/mTBI diagnosis (i.e., to exclude any case of moderate or severe TBI): abnormal brain CT/MRI, GCS < 13 more than 1-hour post-injury, hospitalization >48 hours. Approximately two-thirds of the patient cohort presented with sports-related concussions. The other patients presented with concussion/mTBI related to a variety of other mechanisms, including work place injuries, motor vehicle accidents (MVAs) and falls. The independent variable in the assessment of risk factor was concussion/mTBI. Outcome measures were epilepsy incidence (dependent variable) and prevalence.

One investigator (CH) reviewed the charts and intake forms of all 330 patients and identified any patient whose medical documentation included mention of "epilepsy," "seizure," "convulsion," or related terms (e.g., "black–out," "aura"). All positively identified cases were reviewed in detail by an epileptologist (RW).

A case study of a UHN epilepsy clinic patient with a diagnosis of post-traumatic epilepsy secondary to sports-related concussion is presented to illustrate diagnostic issues that may arise in the setting of epilepsy and a prior history of concussion.

UHN Research Ethics Board approval was obtained for longitudinal study of this post-concussion patient cohort.

RESULTS

The mean number of concussions per patient was 3.3 (±2.5); the median was 3 concussions per patient. Mean age at first clinic visit was 28 years (±14.7). Mean follow-up after last concussion was 1.4 years (±3.0). Mean follow-up after first concussion was 7.6 years (±10.8); median follow-up after first concussion was 3.1 years (interquartile range: 1.0-9.1 years). Minimum follow-up was 1 month (nine patients). Eighty-seven percent of patients had follow-up >6 months.

Eight patients were identified whose medical records included mention of the occurrence of seizures or convulsions or a possible diagnosis of epilepsy. Detailed epileptological chart review of these patients' histories and investigations revealed none that could be considered to have a definite diagnosis of epilepsy.

Specifically, three patients had vague histories of episodes not suggestive of epileptic seizures: one with multimodality, prolonged (up to 1 hour) hallucinations and normal EEG; one with multifocal paraesthesiae, seizures endorsed on the clinic intake form and described as "sudden body spasm related to twitching muscles"; and one with a single non-convulsive "black-out" and normal EEG.

One patient had a clear history of syncope and syncopal convulsion.

Two patients had classical histories of a concussive convulsion, both hockey players: a 22-year-old with immediate loss of

consciousness and convulsion on the ice; and a 15-year-old with immediate loss of consciousness and convulsion on the ice after the second of three sports-related concussions sustained over a 6-month period (the third concussion occurred 2 months after second).

The remaining two patients required more extensive review and their cases are presented in more detail.

Case 1

A 22-year-old woman, rugby player, estimated she had sustained "at least 10" concussions from grade 11 high school through first year university. Family history of two convulsions in a sibling (at ages 11 and 13 years), with unclear diagnosis and no medical treatment. The patient's most recent concussion (rugby-related) was possibly associated with concussive convulsion on the field. Two to three months after that concussion she began to experience spells of *déjà-vu* lasting 30-60 seconds, followed by throbbing headaches, recurring intermittently over many months. Assessed by two different epileptologists (one UHN and one non-UHN neurologist), both unconvinced of epilepsy (differential diagnosis thought to be migraine and/or anxiety). MRIs and routine and sleep-deprived EEGs were normal. No anti-epileptic medication was prescribed. The spells ceased spontaneously 8 months before last follow-up with the second epileptologist, along with resolution of other post-concussion symptoms. Migraine, in retrospect, would seem the most likely diagnosis.

Case 2

A 17-year-old woman with a history of five sports-related concussions over 4 years (the first four concussions hockey-related, the fifth, snowboarding). No family history of epilepsy. A single witnessed convulsion occurred in the months between the third and fourth concussions, described as "tonic-clonic movements of all four limbs." She was not seen by a neurologist or epileptologist, and no EEG was obtained. No treatment was prescribed. Four years after the most recent (fifth) concussion, a second, similar episode occurred while getting a tattoo, presumably representing reflex syncope with syncopal convulsion. The latter event makes it highly probable that the first event was also non-epileptic, and most likely a syncopal convulsion.

Thus, no patient in this large ($n = 330$) post-concussion cohort met criteria for a definite diagnosis of epilepsy over a mean follow-up from first concussion of 7.6 years. Compared with current estimates of epilepsy prevalence (6-8/1000 individuals) and annual incidence (0.5-0.7/1000 individuals) in the general population,[39-42] there was no difference in this post-concussion cohort (Yates' $\chi^2 = 0.472$, df 1, $p = 0.49$, using 0.5/1000/year as expected incidence).

Despite the inability to identify a single incident case of epilepsy in our large cohort of post-concussion patients, it cannot be ignored that some patients with incontrovertible seizures carry the diagnosis of post-traumatic, post-concussion, epilepsy. To illustrate this and some of the relevant diagnostic issues that may challenge the epilepsy specialist, rather than the concussion specialist, we describe a patient referred to the UHN epilepsy clinic with a long-standing diagnosis of medically refractory post-traumatic epilepsy secondary to sports-related concussion.
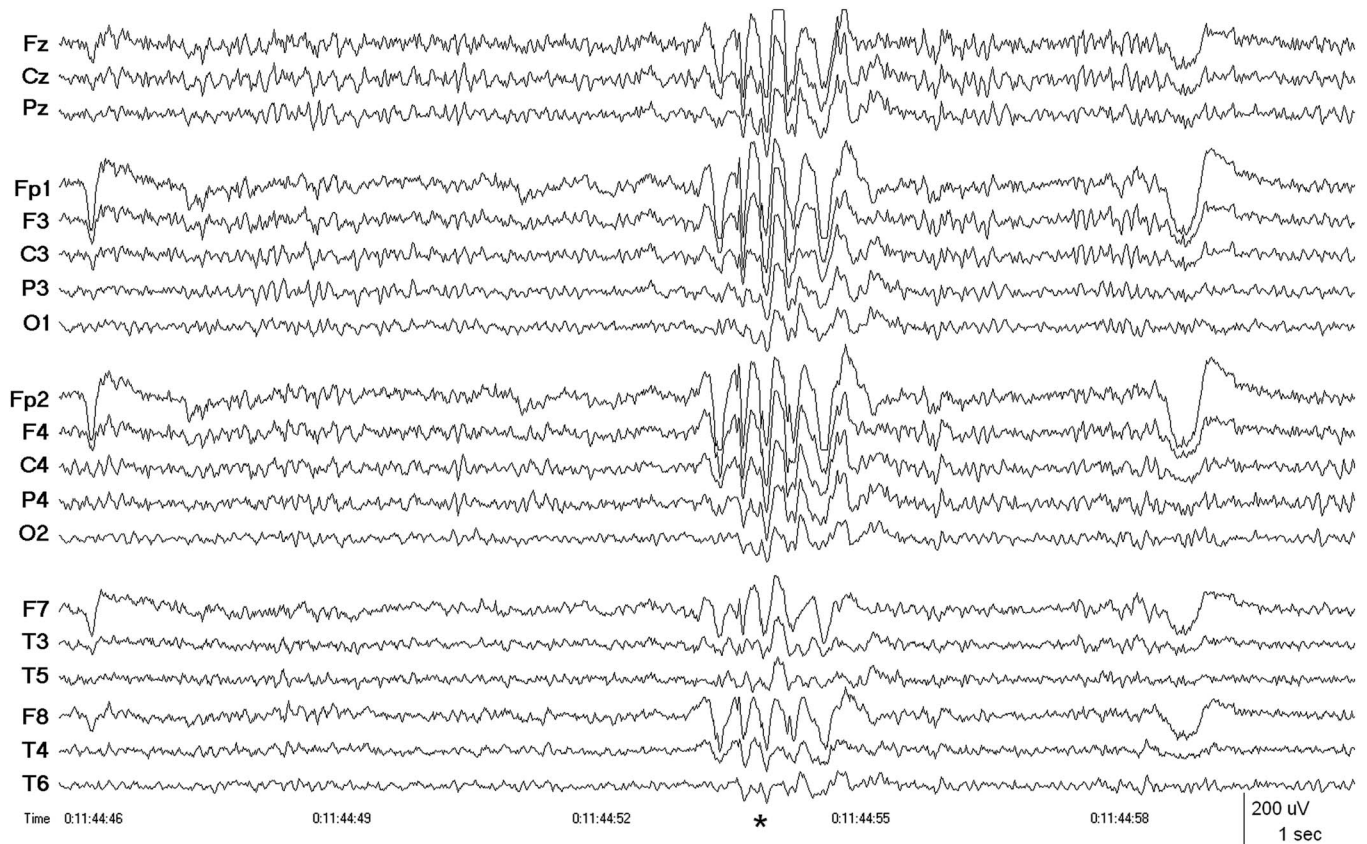
Case 3

A 43-year-old man with a history of soccer-related concussion at age 12 years. Family history of seizures in a cousin that remitted in later life; the same cousin's son also has epilepsy. Approximately 1 year after the patient's concussion he had a first generalized tonic-clonic seizure. The following year he was involved in an MVA and suffered another mTBI, possibly associated with a skull fracture but no intracranial pathology. He then began to experience generalized tonic-clonic seizures approximately once every 8 months for many years, despite anti-epileptic medication treatment with phenytoin (400-500 mg daily), carbamazepine (600 mg tid), and clobazam (30 mg daily) in combination. The presumptive diagnosis was post-traumatic epilepsy. Over the past decade, generalized tonic-clonic seizures remitted but he began to have, four or five times a year, prolonged confusional episodes lasting an hour or more, preceded by a sense of "not feeling myself" or "dizziness," followed by deep somnolence lasting up to 24 hours, during which his wife could administer his medications, but for which time period he was subsequently entirely amnestic.

To investigate the nature of these confusional spells, the patient was admitted for video-EEG monitoring, which revealed bursts of generalized, bilaterally synchronous and symmetrical 3-4 Hz spike and wave (Figure 1) and polyspike and wave activity consistent with a primary generalized epilepsy. After reduction of anti-epileptic medications, the generalized epileptiform activity became increasingly more active, culminating in three tonic-clonic seizures occurring over 4 hours on the third day of admission, all clinically and electrographically generalized from onset. For more than 1 hour before the first motor seizure and continuing between and after each of the convulsions, abundant generalized periodic polyspike activity was recorded, during which time the patient was mildly confused and lethargic. He later remembered feeling unwell before the first tonic-clonic seizure, when the generalized spike and wave and polyspike and wave activity had become increasingly abundant. Anti-epileptic medications were resumed, substituting valproic acid for carbamazepine, and the patient was discharged from the epilepsy monitoring unit after 5 days of recording, during which time no evidence of a focal epileptiform or non-epileptiform abnormality was found.

The patient has been seizure-free with therapeutic levels of valproic acid (1750 mg daily dosage) for more than a year since the video-EEG investigation. He continues to take phenytoin (400 mg daily) and clobazam (30 mg daily), declining for the time being a proposal to consider tapering the phenytoin dosage. Rather than post-traumatic epilepsy, this patient had suffered for three decades from idiopathic primary generalized epilepsy.

DISCUSSION

Epidemiologic studies have indicated that mTBI, or concussion, is associated with an approximately twofold increased risk for epilepsy—sixfold in patients with a family history of epilepsy.[2,3,5,7,19,20] Nonetheless, the internal validity of these findings may be open to question. In particular, classification of TBI severity in most population-based studies has been imprecise, in some based solely on registry ICD codes[5,7] that have been shown to have low accuracy for TBI classification, especially for mTBI.[12,22-24] Furthermore, the methods of some epidemiologic

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Figure 1: *Case 3, patient with 30-year history of medically refractory presumed post-traumatic focal epilepsy attributed to sports-related concussion. EEG showing burst of generalized, bilaterally synchronous 3 Hz spike and wave activity (*) diagnostic of a primary (idiopathic) generalized epilepsy. There were no focal abnormalities during 5 days of continuous video-EEG monitoring. Patient seizure-free (follow-up >1 year) after initiation of treatment with valproic acid. Linked ears (A1-A2) referential montage. Low-frequency filter 0.5 Hz, high-frequency filter 70 Hz.*

studies would have identified patients with concussive convulsions[2,3,7,19] or exacerbation of pre-existing epilepsy[5] as incident cases of post-traumatic epilepsy.

No incident case of epilepsy was identified among our 330 post-concussion patients during the mean follow-up period of 7.6 years, a finding indicating no difference in the annual incidence of epilepsy between our patient cohort and the general population ($p = 0.49$). Nevertheless, it must be acknowledged that our cohort study was slightly underpowered to detect a twofold increase in incidence above the general population (*post hoc* power analysis suggested a sample size of $n = 380$ to avoid Type II error), which may explain in part our inability to confirm the increased risk of epilepsy after mTBI found in population-based studies. However, compared with population-based studies, one advantage of our cohort study is that the diagnostic classification of mTBI/concussion was strictly defined, eliminating the heterogeneity of TBI classification inherent in previous epidemiologic studies. Population-based studies have not heretofore been able to reliably exclude cases of moderate or severe TBI, which could also explain our divergent findings regarding the risk of epilepsy after mTBI, that is, the different findings may reflect our cohort's strictly homogeneous mTBI classification. In addition, our methods allowed us to exclude cases of concussive convulsions as incident epilepsy, and also to exclude cases of exacerbation of pre-existing epilepsy by mTBI (although no such cases appeared in our post-concussion cohort).

The prevalence of epilepsy in our post-concussion cohort was lower than in the general population, possibly owing to an over-representation of athletes among our patients. However, there is no evidence that athletes are less likely than non-athletes to suffer from post-traumatic epilepsy, and so for the aim of this study—to analyze the incidence of epilepsy in post-concussion patients in whom concussion was strictly defined—a lower baseline epilepsy prevalence was not important.

Clinical perspectives on the epidemiologic data

In the epilepsy clinic, it is not uncommon for patients to describe one or more past head injuries as the suspected cause of their epilepsy. It is also not uncommon to find in these same patients, upon investigation with neuroimaging and EEG, evidence of a focal epilepsy associated with structural abnormalities such as hippocampal sclerosis or developmental cortical malformations, that is, well-defined epilepsy etiologies predating the recollected head injuries. If medical registry documentation (e.g., upon presentation to an emergency department) existed for any of the head injuries, patients such as these would be imprecisely identified as incident cases of post-traumatic epilepsy by the methods of registry data set-based epidemiological studies.

Similarly, patients with primary generalized epilepsy and a history of mTBI antedating a first seizure (e.g., Case 3 in this

paper) would also be subject to capture as incident cases of post-traumatic epilepsy in epidemiologic studies. Given the observation that mTBI can exacerbate pre-existing, clinically manifest epilepsy,[38] it is conceivable that mTBI could also unmask latent, for example, primary generalized, epilepsy. This might account for much of the increased risk of epilepsy after mTBI that has been described in individuals with a family history of epilepsy. Case 3 may represent an example of a latent primary generalized epilepsy revealed by a concussion, although the possibility that his epilepsy would have manifested spontaneously around the same time, irrespective of the mTBI, cannot be excluded. Either way, whether unmasked by the mTBI or emerging spontaneously, the onset of seizures after a concussion would have classified his case as incident post-traumatic epilepsy in epidemiologic studies, which would be a clear misrepresentation of a genetically predetermined epilepsy. Even more importantly, in the clinical realm, unquestioning acceptance of concussion as a plausible risk factor for epilepsy resulted in misdiagnosis of his generalized epilepsy syndrome, and 30 years of incomplete seizure control, before the correct diagnosis was made and seizure freedom attained after a simple change of medications.

Another case report has been published describing an elite rugby player with new-onset seizures—and the attendant assumption of a focal post-traumatic epilepsy—in whom the diagnosis turned out be an easily treatable 3 Hz polyspike and wave generalized epilepsy, emphasizing the need to avoid a presumption of post-traumatic epilepsy in individuals with a history of concussion/mTBI.[43]

Limitations

A main limitation of our study is the length of follow-up after initial concussion. Although the largest and longest study of its kind, the mean patient follow-up of 7.6 years leaves open the possibility that concussion/mTBI could be a risk factor for the *de novo* development of epilepsy long removed from the initial head injury, for example, 10 years or more post-injury. Indeed, some epidemiologic studies have described a small increased risk of epilepsy to persist >10 years after mTBI,[5,7,20] although other studies found no increased risk beyond 5 years.[2,3,19] All epidemiologic studies have, however, reported the maximum increase in relative risk to be within the first few years post-injury, particularly within the first 6-12 months,[2,3,5,7,19,20] and a large majority of our patients had follow-up that covered this period of previously described peak relative risk.

Another limitation is the total number of patients in the cohort. The advantages of the cohort in terms of uniformity of concussion/mTBI diagnosis are clear, however, even a cohort as large as this was slightly underpowered for the detection of small increases in relative risk of epilepsy, when compared with population-based studies. Future investigation of a larger cohort drawn from either a multi-specialist clinic or a multi-center study would be ideal.

Although many of the patients in our predominantly sports-related concussion cohort had sustained multiple concussions (mean 3.3/patient), in the absence of any incident cases of epilepsy we could not specifically address the question of whether multiple concussions confer an increased relative risk. Our findings suggest that a small number of concussions does not increase

the risk for epilepsy, however, the shorter mean follow-up after last concussion (1.4 years) limits the strength of this conclusion.

Clinical perspectives on this study's data

The results of this cohort study pertain specifically to patients with an accurate diagnosis of concussion/mTBI, and the findings cannot be extended to patients with moderate or severe TBI. In the clinic, however, patients referred for concussion may actually have suffered, in some cases, a more severe TBI marked by structural damage visible on CT or MRI. Our retrospective cohort study was not designed to address the question of neuroimaging utilization in patients with TBI. Nevertheless, absence of structural abnormality on brain CT/MRI is part of the diagnostic criteria for concussion/mTBI.[14,15] In assembling the cohort for this study, 26 patients initially referred for concussion were excluded because their neuroimaging studies showed abnormalities, most commonly hemorrhagic contusions or encephalomalacia in the frontal or temporal regions. For the sake of interest, we did look to see how many of these excluded patients had evidence of post-traumatic seizures or epilepsy and found four patients who did: two with a single early post-traumatic seizure and two with definite post-traumatic focal epilepsy. These four patients all had bilateral contusions and/or encephalomalacia plus, in one case, a subdural hematoma. It is thus easy to understand how clinical misclassification of moderate-severe TBI as concussion can confound an accurate appreciation of the risk of epilepsy after mTBI.

Current recommendations suggest that patients with a clear history of concussive convulsion require no further epilepsy investigation (e.g., neuroimaging or EEG).[34,36] Notwithstanding, if there is any question as to the exact circumstances of the convulsion—most importantly, whether or not it occurred within 2 seconds of impact—then it would seem reasonable to obtain neuroimaging to exclude more severe TBI.

In the concussion clinic, patients with a history suggestive of epileptic seizures (and particularly those with a family history of epilepsy) should ideally be investigated with high-quality EEG or video-EEG (to confirm an epilepsy diagnosis) and high-quality CT/MRI, with the expectation that either: (a) traumatic structural abnormalities are present (and that the head injury was therefore more severe than concussion/mTBI), or that (b) the patient may have a pre-existing epileptic disorder, for example, primary generalized epilepsy. Normal EEG and MRI investigations in a post-concussion patient effectively exclude the diagnostic possibility of epilepsy.

In the epilepsy and general neurology clinic, a past history of concussion should not easily be accepted as a plausible risk factor for epilepsy. Patients with epilepsy should be investigated with high-quality, high resolution MRI and EEG or video-EEG to arrive at an accurate diagnosis of epilepsy type (focal or generalized) and etiology (structural or genetic/idiopathic). A post-traumatic etiology for epilepsy should not be presumed in a patient with a past history of strictly defined concussion/mTBI.

Conclusion

In this large cohort of post-concussion patients we found no increased incidence of epilepsy. For at least the first 5-10 years post-injury, concussion/mTBI should not be considered a

significant risk factor for epilepsy. In patients with epilepsy and a past history of concussion, the epilepsy should not be presumed to be post-traumatic.

STATEMENT OF AUTHORSHIP

RW conceived the study and wrote the manuscript. All authors contributed significantly to data collection and critical review of the manuscript, and all authors approved the final version.

DISCLOSURES

The findings of this study were presented in abstract form at the 5th International Conference on Concussion in Sport, Berlin, Germany, October 2016. The authors have no other conflicts of interest to declare.

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