Risky Business: Traumatic Brain Injury and Epilepsy

Repeated Traumatic Brain Injury and Risk of Epilepsy: A Danish Nationwide Cohort Study

Lolk K, Dreier JW, Christensen J. *Brain*. 2021;awaa448. doi:10.1093/brain/awaa448

Traumatic brain injury is associated with increased risk of epilepsy, but the importance of repeated traumatic brain injuries has not yet been established. We performed a nationwide population-based cohort study of 2 476 905 individuals born in Denmark between 1977 and 2016. We estimated hazard ratios (HRs) and the cumulative incidence of epilepsy following traumatic brain injury using Cox and competing risk regression, respectively. To estimate the cumulative incidence of epilepsy in the population without traumatic brain injury, we matched 10 controls for each subject with traumatic brain injury on year of birth, sex, and date of brain insult in the index person. In the cohort, traumatic brain injury was sustained by 167 051 subjects (71 162 females and 95 889 males), and 37 200 individuals developed epilepsy (17 905 females and 19 295 males). Compared with subjects without traumatic brain injury, the relative risk of epilepsy increased after a first traumatic brain injury (HR: 2.04, 95% confidence interval (CI): 1.96-2.13) and even more after a second traumatic brain injury (HR: 4.45, 95% CI: 4.09-4.84). The risk increased with the severity of the first and the second traumatic brain injury, most notably after severe traumatic brain injuries. Females were more likely than males to develop epilepsy after mild traumatic brain injury (HR: 2.13, 95% CI: 2.00-2.28 vs HR: 1.77, 95% CI: 1.66-1.88; $P < .0001$); in contrast, males were more likely than females to develop epilepsy after severe traumatic brain injury (HR: 5.00, 95% CI: 4.31-5.80 vs HR: 3.21, 95% CI: 2.56-4.03; $P = .0012$). The risk remained increased for decades after the traumatic brain injury. This knowledge may inform efforts to prevent the development of post-traumatic epilepsy.

Commentary

Prognostication is a key task for epilepsy clinicians. Yet, at the moment of a patient visit, we invariably lack the luxury of hindsight regarding which patients with a particular seizure risk factor will go on to develop epilepsy. Long-term clinical epidemiological data provide the closest we have to a crystal ball in absence of clairvoyance or a decades-skipping time machine. Fortunately, Scandinavian countries keep outstanding tabs on their populations providing invaluable long-term prognostic information informed by decades of real-world data encompassing millions of lives.

Here, Lolk et al[1] harnessed their access to superb population monitoring in Denmark to answer a set of important prognostic questions: (1) What is the risk of future epilepsy following a first or second traumatic brain injury (TBI)? and (2) What TBI or other patient factors modify that risk? Surely, TBI has been recognized as an epilepsy risk factor since literally thousands of years B.C.[2] Yet, the authors filled several knowledge gaps such as the effect of a single versus repeated TBI.

They followed nearly 2.5 million Danes born between 1977 and 2016 on average through young adulthood, with a mere 4%

loss to follow-up or death. They identified TBI and epilepsy via hospital-based *International Classification of Diseases* (ICD) codes, plus outpatient/emergency department codes available for only about the second half of their follow-up. Approximately 34 000/1.7 million without a TBI developed epilepsy, whereas approximately 3000/167 000 with a TBI did. This resulted in a 20-year cumulative risk of developing epilepsy of 1% in age- and sex-matched controls without a TBI, compared with 2% and 3% following the first or second mild TBI, respectively, 2% following the first skull fracture, and 6% and 15% following the first or second severe TBI, respectively. Adjusted HRs ranged from 1.9 (95% CI: 1.8-2.0) after a first mild TBI, to 16 (95% CI: 13-20) after a second severe TBI. Psychiatric diagnoses and family history also increased epilepsy risk. Despite the unchangeable limitation that they lacked outpatient/emergency department information for much of their study (and the performance of ICD codes for identifying TBIs is not entirely clear from the methods), multitudinous sensitivity analyses addressing misclassification or reverse causation (ie, modifying the exact number or time course of ICD codes to be counted as a TBI or epilepsy) changed little.

Similarly, little changed when the authors compared those with a TBI to those with non-TBI injuries, to equalize unmeasured trauma-related risk factors.

So, how does this information help us clinically? This study lays transparent the long-term risks of developing epilepsy under a range of TBI types, among children through young adults, with the narrowest CIs and least selection bias that one will find on the planet for this question. The data also resoundingly conclude that, as we already knew, risk factor is not disease. The maximally 15% long-term cumulative incidence in the most severe studied group falls well short of the expert threshold of 60% to declare epilepsy.[3] Available evidence does support prophylactic phenytoin to reduce seizures within 7 days of a severe TBI.[4] However, 7-day decisions are quite different from 20-year decisions. Furthermore, trauma is only responsible for about $\sim 6\%$ of all epilepsy,[5] these documented risks fill in pretest probability but lack stratification by electroencephalogram or magnetic resonance imaging findings to fill in posttest probability, only a subset of epilepsy cases were presumably disabling or refractory though this portion is unknowable from the data, and for the epilepsy specialist predicting future epilepsy is often moot given our patients frequently already have epilepsy by the time they see us. All of this is certainly not to say that risk estimation is unimportant. Clearly, it is. Or to say that this study does not help us. It does. But this is to say that even with this study's excellent long-term population-wide follow-up with extensive subgroup and sensitivity analyses, the direct implications are not straightforward other than enhancing good preventive counseling, and not overreacting to risk factors in absence of a known seizure history.

With epidemiological data, questions always remain regarding the degree to which studied effects are "causal." Nobody would bat an eye that more or worse TBIs cause pathology elevating epilepsy risk. Still, there are some peculiarities of the data, like how first skull fracture (HR: 1.7) was less predictive than mild TBI (HR: 1.9); not at all particular to this study, "big data" always runs the risk of detecting in-sample noise rather than signal which would not be reproduced in an external sample. Also, the investigators for example found that epilepsy risk increased with older age at most recent TBI. The dataset adjusted for alcohol and drug abuse by *ICD* codes, but *ICD* codes alone seem unlikely to fully capture such person-level habits which change between childhood and young adulthood, which tempers any biologically based conclusions about the developing brain itself. And, the article presents conflicting conclusions regarding the interaction between family history or psychiatric disease with TBI on the additive versus multiplicative scales. Nonetheless, in response to the question "Is it causal?" My response would be, "Does it matter?" In the end, whenever a study marginally improves our crystal ball from a set of easily measured variables correlated with the outcome

(barring meaningful overfitting [inevitably, some], mismeasurement [inevitably, some], or model misspecification [probably not, given the investigators confirmed the proportional hazards assumption and loss to follow-up was trivial]) without overinterpreting causality, that is good enough for me.

Finally, it is also important to note that risk prediction is only one side of the coin; how we communicate that risk to patients matters a great deal. For example, simply describing an outcome chance as "5%" rather than "5 in 100" changes how a patient manipulates that information, especially in patients with lower numeracy or health literacy who understands the concept of percentages less well than the clinician does.[6] Good risk communication involves absolute (1% veruss 2-3%) rather than relative risks (HR 2-3), some experts suggest using more concrete frequencies (5 in 100) rather than percentages (5%), and displaying such information using pictographs (which we never do) rather than words (usual method) to enhance a patient's understanding.[6] Of course this study deals with prognosis rather than any treatment decision. Still, given the great lengths Lolk et al have gone to provide us this best-available risk prediction, if we were going to provide these data to patients for treatment or other lifestyle decisions, we must now be thoughtful consumers of medical literature by remaining cognizant that how we relay such information makes a difference.

By Samuel W Terman 🄳

ORCID iD

Samuel W Terman 🄳 https://orcid.org/0000-0001-6179-9467

References

1. Lolk K, Dreier JW, Christensen J. Repeated traumatic brain injury and risk of epilepsy: a Danish nationwide cohort study. *Brain*. 2021:1-10. doi:10.1093/brain/awaa448
2. Lowenstein DH. Epilepsy after head injury: an overview. *Epilepsia*. 2009;50(suppl 2):4-9. doi:10.1111/j.1528-1167.2008.02004.x
3. Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482. doi:10.1111/epi.12550
4. Chang BS, Lowenstein DH. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. 2003;60(1):10-16.
5. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia*. 1993;34(3):453-468.
6. Fagerlin A, Zikmund-Fisher BJ, Ubel PA. Helping patients decide: ten steps to better risk communication. *J Natl Cancer Inst*. 2011;103(19):1436-1443. doi:10.1093/jnci/djr318