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Short report

Adult-onset epilepsy and risk of traumatic brain injury: a nationwide cohort study

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ABSTRACT

Background A knowledge gap exists regarding the risk of traumatic brain injury (TBI) in patients with epilepsy.

Methods Patients with adult-onset epilepsy during 2005–2018 in Finland were studied using retrospective longitudinal national registry-linkage design. Patients with epilepsy (n=35 686; 51% men; mean age 56.6 years) were 1:1 matched to non-epileptic controls by age, sex, comorbidity burden and cohort entry year. The primary outcome was TBI leading to admission or death, secondary outcomes were TBI admission, fatal TBI, acute neurosurgical operations (ANOs) for TBI and TBI recurrence.

Results The cumulative rate of the primary endpoint was 1.2% at 1 year, 5.6% at 10 years and 7.3% at 14 years in the epilepsy group versus 2.9% at 14 years in the matched controls (HR=3.77; p<0.0001). Epilepsy was associated with increased risk of TBI admission (6.9% vs 2.7%; HR=3.96; p<0.0001), ANOs (1.3% vs 0.4%; HR=7.00; p<0.0001) and fatal TBI (1.3% vs 0.5%; HR=3.82; p<0.0001), during follow-up. Competing risk analyses confirmed the association of epilepsy with all outcomes (p<0.0001). Epilepsy was associated with TBI recurrence during follow-up (HR 1.72; p=0.002).

Conclusion Patients with adult-onset epilepsy have a significantly increased risk of severe and fatal TBI. The results underline the importance of TBI prevention in epilepsy.

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of lost work years, disability and mortality in all age groups. An important deficit resulting from TBI is post-traumatic epilepsy.¹ The literature addressing the issue from the other direction is sparse, although some studies have examined the risk of extracranial injury in patients with epilepsy.^{2,3} However, little is known about the risk of TBI in patients with epilepsy.⁴ Notably, no large-scale population-based or nationwide studies are available. We conducted a comprehensive population-based risk assessment of TBI admissions, TBI-related acute neurosurgical operations (ANOs) and TBI-related deaths in patients with adult-onset epilepsy during a 14-year study period. We used a matched, population-based cohort of patients without epilepsy as a reference population.

METHODS

Study population

Adult patients with new-onset epilepsy in Finland during 2005–2018 were identified from a national database of entitlements to special reimbursements for prescription medications (entitlement code 111). Medications for epilepsy are available only by

prescription in Finland and are state sponsored given the entitlement. Adult subjects with reimbursement entitlement for hypothyroidism (code 104; 42.9% of matched controls), inflammatory bowel disease (code 208; 40.6%) or gout (code 212; 16.5%) were selected as non-epileptic controls. Patients who had contact with a specialist (regardless of specialty or route) or an emergency department visit during the study period were included. Our study covers 96% of all adult epilepsy cases during the study period.⁵ Patients and controls with TBI admission within 1 year prior to reimbursement were excluded (0.1% of controls and 4.4% of epilepsy patients).

Outcomes and definitions

The primary outcome was a composite of TBI admission or fatal TBI. Secondary outcomes were TBI admission, fatal TBI and ANO for TBI. Admissions and ANOs were identified from the Care Register for Health Care (CRHC) and deaths from the national cause-of-death registry.⁶ A TBI admission was defined as a ward-treatment period with ICD-10 code S06.* as the primary diagnosis.⁷ A fatal TBI was defined as S06.* as any cause of death.⁸ Patients with operated chronic subdural haematoma (ICD-10 codes S06.5 or I62.0 with operation for evacuation of chronic subdural haematoma (NOMESCO operational codes AAD10 or AAD12)) were not included in the study. Only true TBI diagnoses were included, and skull base or calvarial fractures alone were not included. Recurrence of TBI was studied in the subgroup of patients with an index TBI admission (online supplemental file 1). Validity of the ICD-10 TBI codes has been earlier studied.⁷

Neurosurgical operation for a TBI was defined as TBI admission with relevant operational codes.⁹ Follow-up ended on 31 December 2018 and was complete for all study patients. The median follow-up was 4.8 years (IQR 1.9–8.6; max 14.0). The Charlson Comorbidity Index (CCI)¹⁰ at baseline was calculated using a combination of the CRHC, entitlement data and data from the Finnish Cancer Registry.¹¹

Study data and permissions

The study data were obtained from Findata (permission no: THL/164/14.02.00/2021) and Statistics Finland (permission no: TK/923/07.03.00/2022). The participants were not contacted. The legal basis for processing personal data is public interest and scientific research (EU General Data Protection Regulation 2016/679, Article 6 (1)(e) and Article 9 (2)(j); Data Protection Act, Sections 4 and 6).

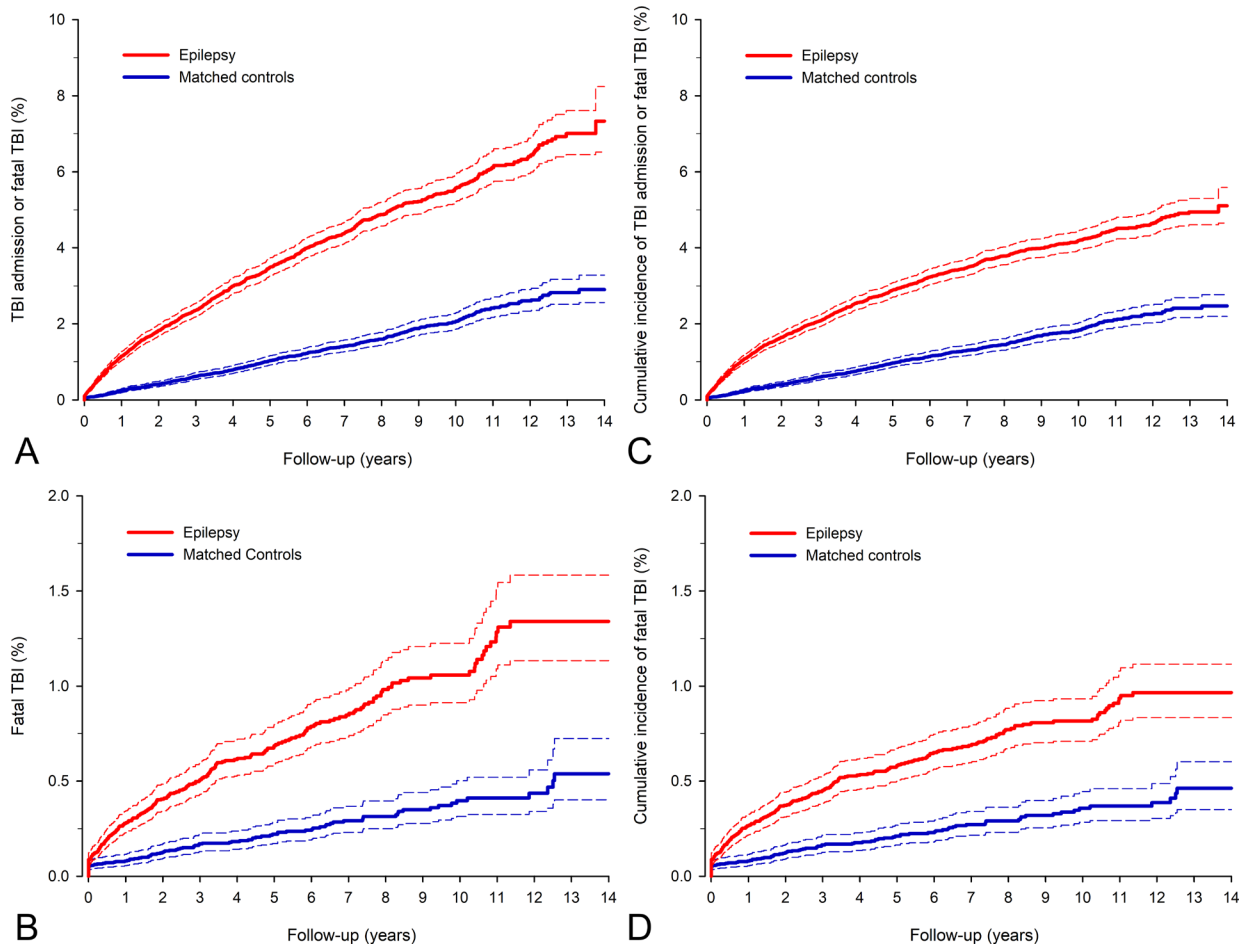


Figure 1 Traumatic brain injury (TBI) admission or death, cause-specific analyses (A), fatal TBI, cause-specific analyses (B), cumulative incidence of TBI admission or death, competing risk analyses (C) and fatal TBI, competing risk analyses (D) in patients with adult-onset epilepsy and matched controls. Please note the difference in the y-axis. Dashed lines represent 95% CIs.

Statistical analysis

Propensity scores were created by logistic regression based on baseline age, sex, age*sex, CCI and cohort entry year. These scores were used to match patients with epilepsy 1:1 with controls by the nearest neighbour method. The standardised mean difference was ≤ 0.16 between study groups for all variables. Outcomes were studied using the Kaplan-Meier estimator and Cox regression with cause-specific design. Additional sensitivity analyses were performed with cumulative incidence function and Fine-Gray models accounting for competing risk by non-endpoint-specific death. The results are presented as mean, median, percentage, HR or subdistribution HR (sHR) with a 95% CI, \pm SD or IQR. Statistical significance was inferred at $p < 0.05$. SAS V.9.4 was used for the analyses.

RESULTS

The study population included 35 686 adult patients with epilepsy (51.4% men) and 35 686 matched controls. The mean age of patients with new-onset epilepsy was 56.6 years (SD 20.4, range 16–102) and the median CCI was 1 (IQR 0–2, range 0–16).

The primary outcome occurred in 1142, TBI admission in 1046, ANO in 225 and fatal TBI in 234 patients with epilepsy during the 14-year follow-up. The cumulative rate of TBI admission or death in patients with epilepsy was 1.2% at 1 year, 3.5% at 5 years, 5.6% at 10 years and 7.3% at 14 years (figure 1A). The corresponding rates in controls were 0.2%, 1.0%, 2.1% and 2.9%, respectively. Epilepsy was associated with TBI admission or death at HR 3.77 (CI

3.37 to 4.23; $p < 0.0001$) during follow-up when compared with matched non-epileptic controls. The cumulative rate of TBI admission was 6.9% in the epilepsy group and 2.7% in the control group (HR 3.96; CI 3.50 to 4.48; $p < 0.0001$) at 14 years. The fatal TBI rate was 0.3% at 1 year, 0.7% at 5 years, 1.1% at 10 years and 1.3% at 14 years in the epilepsy group and 0.5% at 14 years in the control group (HR 3.82; CI 2.97 to 4.92; $p < 0.0001$) (figure 1B). ANOs for TBI were performed in 1.3% of the patients with epilepsy and 0.4% of the controls during the follow-up (HR 7.00; CI 4.93 to 9.93; $p < 0.0001$). Epilepsy was associated with TBI recurrence during 10-year follow-up after index TBI admission (HR 1.72; $p = 0.002$) (online supplemental file 2).

The results of the competing risk analyses agreed with the primary cause-specific analyses (figure 1C,D). The cumulative incidence of TBI admission or death (5.1% in the epilepsy group vs 2.5% in the controls; sHR 2.57; CI 2.34 to 2.81; $p < 0.0001$), TBI admission (4.8% vs 2.3%; sHR 2.63; CI 2.39 to 2.89; $p < 0.0001$), fatal TBI (1.0% vs 0.5%; sHR 2.56; CI 2.10 to 3.12; $p < 0.0001$) and ANOs (0.9% vs 0.4%; sHR 3.96; CI 3.08 to 5.09; $p < 0.0001$) were all higher in patients with epilepsy than in the matched controls during the 14-year follow-up, after accounting for the competing risk of non-endpoint-specific death.

DISCUSSION

In this population-based study using matched cohorts, we showed that epilepsy is associated with an increased risk of TBI admissions,

ANOs, TBI-related deaths and TBI recurrence. The HRs were four-fold to sevenfold in patients with epilepsy compared with controls. The competing risk analyses confirmed the association between epilepsy and these outcomes.

The current literature dealing with this subject is minimal. However, some comparisons can be made. A regional Swedish study reported that epilepsy was associated with mild TBI (adjHR=1.42) and severe TBI (adjHR=2.07) compared with non-epileptic controls.¹² A regional study from the USA reported that the hazard of recurrent TBI for persons with epilepsy was 2.3 times higher than in persons without epilepsy.¹³ A previous study examining TBI severity in patients with and without previous epilepsy reported a 50% increased risk of suffering a more severe TBI in patients with epilepsy than in patients without a history of epilepsy.¹⁴ Another study reported a 17% increased risk of severe TBI in patients with epilepsy.¹⁵ It has been reported that patients with severe drug-refractory epilepsy on antiepileptic polytherapy are hospitalised more frequently than the general population for injuries, including head injuries, and have a sevenfold increased mortality rate.¹⁶ The current results echo the previous findings and indicate even more serious impact of epilepsy on TBI and its severity.

The strengths of this study lie in the usage of national registries required by law, which provide a complete picture of the Finnish population. The validity of epilepsy and TBI diagnoses has been demonstrated previously.^{5–7} We selected non-neurological patient groups as controls so that they would not have an increased tendency to fall. A limitation of the study is that only epilepsy patients who had contact with a specialist or an emergency department visit during the study period were included, but as noted previously, the cohort includes 96% of all adult epilepsy cases. Because of the administrative nature of the data, we could not assess the severity of epilepsy. We did not analyse the mechanisms of injury, and it is worth noting that the injuries of epilepsy patients are not necessarily related to the fall but to the seizure itself. Although the validity of TBI diagnoses has been shown to be excellent, we were unable to exclude patients with non-operated chronic subdural haematomas due to limitations in the ICD-10 coding.

Compared with the general population, people with epilepsy are at an increased risk for numerous injuries. This increased risk of injury in patients with epilepsy is mostly related to seizure control and medication side effects. Comorbid conditions that affect cognition, attention or gait are common in people with epilepsy and increase their injury risk.¹²

CONCLUSION

The current results show that epilepsy is associated with an increased risk of admission for TBI, TBI-related death, ANOs and TBI recurrence compared with controls. The cumulative incidence of these outcomes was significantly higher in patients with epilepsy during the follow-up. These results underline the importance of head injury prevention and adequate medication in these patients.

Contributors JPP: Drafting and revising the manuscript, study concept and design, interpretation of data. JOR: Revision of the manuscript for content, interpretation of data. VK: Drafting and revising the manuscript, acquisition of data, study concept or design, analysis or interpretation of data. VK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests JPP has received a speaker fee (The Finnish Medical Association). JOR has received scientific consultancy fees (Merck and Sandoz), speaker fees (Merck, Biogen Idec, UCB Pharma and Bayer), travel grants and congress sponsorship (BMS, Sanofi Genzyme, TEVA and Bayer) and holds shares (Medbase, Turku). VK has received a scientific consultancy fee (AstraZeneca), speaker fee (Bayer) and travel grants and congress sponsorship (AstraZeneca, Boehringer Ingelheim, Bayer and Pfizer).

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