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Review

Risk factors for posttraumatic epilepsy: A systematic review and meta-analysis

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ABSTRACT

Objective: A systematic review and meta-analysis was performed to identify risk factors for posttraumatic epilepsy (PTE).
Methods: Two electronic databases (Medline and Embase) were searched to identify studies with a cohort, case-control, or cross-sectional design reporting on epidemiologic evidence regarding risk factors for PTE.
Results: Men had a higher risk of developing PTE than women [relative ratio (RR), 1.32; 95% confidence interval (CI), 1.10–1.59]. A history of alcohol abuse (RR, 2.18; 95% CI, 1.26–3.79), posttraumatic amnesia (RR, 1.31; 95% CI, 1.12–1.53), focal neurologic signs (RR, 1.42; 95% CI, 1.16–1.74), and loss of consciousness at initial traumatic brain injury (TBI) (RR, 1.62; 95% CI, 1.13–2.32) were associated with a greater risk of PTE. TBI-related abnormal neuroimaging findings, including skull fracture (RR, 2.27; 95% CI, 1.49–3.44), midline shift (RR, 1.46; 95% CI, 1.14–1.87), brain contusion (RR, 2.35; 95% CI, 1.69–3.28), subdural hemorrhage (RR, 2.00; 95% CI, 1.33–3.01), and intracranial hemorrhage (RR, 2.65; 95% CI, 1.83–3.82) were strong risk factors for PTE. The risk of developing PTE after skull fracture, mild brain injury, and severe brain injury peaked within the first year after TBI, and then gradually decreased. However, a high risk of PTE was sustained for >10 years.
Conclusion: The current meta-analysis identified potential risk factors for PTE. The results may contribute to better prevention strategies and treatments for PTE.

1. Introduction

Traumatic brain injury (TBI) is one of the most serious traumatic diseases, accounting for 1.1–1.7 million emergency room visits and 50,000 deaths every year [1,2]. Posttraumatic epilepsy (PTE) is a well-known sequela of TBI [1,3], and accounts for 5% of all epilepsy in the general population [4,5]. Unfortunately, PTE is strongly associated with a high risk of mortality in children and adults compared to patients who do not experience PTE [6]. Individuals with PTE are also at a significant disadvantage regarding physical, cognitive, and affective issues, which negatively affect functional outcome following TBI [2,4,7].

To date there is no effective prophylaxis for PTE, and prophylactic anticonvulsant drugs do not reduce the risk of PTE [2,5,8]. Identifying risk factors associated with PTE may contribute to the development of new prevention and treatment strategies. Previous studies have reported a variety of risk factors involved in the development of PTE, including skull fracture, severity of TBI, abnormal neuroimaging findings, clinical features in patients with TBI, and time after TBI. However, due to differences in study design, demographics, definitions of PTE and follow-up duration, risk factors for predicting PTE remain unclear.

Here we report a systematic review and meta-analysis to determine PTE-related risk factors.

2. Methods

A systematic review and meta-analysis were conducted according to the guidelines previously published for a meta-analysis of observational studies in epidemiology (MOOSE) [9]. Ethics committee approval did not apply to this study.

2.1. Study selection

Both Medline and Embase electronic databases were searched using predefined terms and search criteria. The inclusion criteria for the meta-analysis were: 1) English publications; 2) case-control, cohort or cross-sectional methodology; 3) epidemiologic evidence regarding the risk factors for PTE reported; and 4) original research with full-text

Abbreviations: PTE, posttraumatic epilepsy; RR, relative ratio; CI, confidence interval; TBI, traumatic brain injury; ASS, acute symptomatic seizure; GCS, Glasgow Coma Scale; PTA, posttraumatic amnesia; CT, computed tomography; MRI, magnetic resonance imaging; MBI, mild brain injury; SBI, severe brain injury; SDH, subdural hemorrhage; EDH, epidural hemorrhage; SAH, subarachnoid hemorrhage; ICH, intracranial hemorrhage; CNS, central nervous system.

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availability. Non-original articles, articles with insufficient data or irrelevant outcome, and single case reports were excluded. There were no restrictions on the time of publication. Two authors (T.X., X.Y.) independently evaluated the retrieved studies according to the selection criteria and manually reviewed the reference lists of retrieved articles to identify additional relevant studies. Discrepancies were resolved by discussion until consensus was reached.

2.2. Data extraction and quality assessment

Data extracted from eligible studies included first author, publication year, country, study design, population demographics, and information [prevalence of PTE in patients with TBI, hazard ratio, risk ratio, odds ratio, and raw data to calculate relative risk (RR)] to evaluate PTE-related risk factors [e.g., gender, prior alcohol abuse, acute symptomatic seizure (ASS), TBI-related clinical findings, etiology of TBI, abnormal neuroimaging findings, clinical severity of TBI, and the Glasgow Coma Scale (GCS) score at initial TBI]. TBI-related clinical findings included posttraumatic amnesia (PTA), focal neurologic signs, and loss of consciousness at initial TBI. Abnormal neuroimaging findings were confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) examination in patients with TBI. Clinical severity of TBI was categorized into mild brain injury (MBI) and severe brain injury (SBI). MBI was defined as brain concussion without structural damage. By contrast, SBI was associated with brain structural damage, including midline shift, brain contusion, subdural hemorrhage (SDH), epidural hemorrhage (EDH), subarachnoid hemorrhage (SAH), and intracranial hemorrhage (ICH).

For the purpose of the current analysis, ASSs were defined as seizures occurring within 7 days after TBI, while unprovoked seizures were defined as seizures occurring after this period [10]. According to the latest clinical definition of epilepsy proposed by the International League Against Epilepsy (ILAE) in 2014, a patient with one unprovoked seizure after TBI should be diagnosed with epilepsy [11]. This recommendation is based on the fact that a patient with a TBI with a single unprovoked seizure is at high risk of another unprovoked seizure in the next ten years [11].

A nine-star system based on the Newcastle-Ottawa Scale (NOS) was used to assess study quality [12].

2.3. Statistical analysis

The overall prevalence of PTE in patients with TBI was assessed, and the RR for each risk factor for PTE was calculated. Additionally, the risk of PTE according to time since first admission with TBI was investigated by subgroup analyses. To assess between-study heterogeneity, the Cochrane Q statistic was calculated. The I^2 statistic was used to quantify the magnitude of heterogeneity [13]. In the absence of statistically significant heterogeneity ($I^2 < 50\%$), the pooled estimate and 95% confidence intervals (CIs) were calculated with a fixed-effects model. Conversely, a random-effects model was used to calculate the pooled estimate when significant heterogeneity was present ($I^2 \geq 50\%$). Subgroup analyses were performed to explore sources of heterogeneity. STATA version 12.0 (StataCorp, College Station, TX, USA) was used for statistical analyses. A p-value <0.05 was considered statistically significant.

3. Results

After omitting duplicates (articles that were returned from both databases searched), 3233 records were identified during our initial search. After omitting articles with non-relevant titles and abstracts, 167 articles with full text were selected for review. Finally, a total of 20 articles met our inclusion criteria [1,3–7,14–27] (Fig. 1).

3.1. Description of studies and qualitative assessment

The 20 studies selected for meta-analysis were published between 1961 and 2015 and contained a total of 111,751 participants. The 20 studies included 16 prospective analyses [1,3–7,14,16–21,23,24,27] and 4 retrospective analyses [15,22,25,26] (Table 1).

Quality scores of the included studies are listed in Table 1. The mean score of the included studies was 6.40 (standard deviation: 1.19; range: 4–8) (Table S1).

3.2. Pooled prevalence of PTE in patients with TBI

The pooled prevalence of PTE in patients with TBI ranged from 1.3% to 53.3%, with a high-level of heterogeneity between the 20 studies ($I^2 = 98.9\%$). According to the random-effects model, the pooled prevalence of PTE in patients with TBI was 15% (95% CI 14%–17%) (Fig. 2).

3.3. Risk factors for PTE

Male patients were more susceptible to PTE than female patients (RR, 1.32; 95% CI, 1.10–1.59). Prior alcohol abuse (RR, 2.18; 95% CI, 1.26–3.79) was associated with an increased risk of developing PTE. For clinical findings in patients with TBIs, PTA (RR, 1.31; 95% CI, 1.12–1.53), focal neurologic signs (RR, 1.42; 95% CI, 1.16–1.74), and loss of consciousness at initial TBI (RR, 1.62; 95% CI, 1.13–2.32) were associated with a greater probability of developing PTE. The risk of developing PTE in patients with ASS was five times greater than in those without ASS after TBI (RR, 5.14; 95% CI, 2.81–9.41). Although the pooled RRs of the GCS score at initial TBI were not statistically significant, there was an overall trend for an association between a low GCS score and a high risk of developing PTE. Subgroup analyses of abnormal neuroimaging findings found that skull fracture (RR, 2.27; 95% CI, 1.49–3.44), midline shift (RR, 1.46; 95% CI, 1.14–1.87), brain contusion (RR, 2.35; 95% CI, 1.69–3.28), SDH (RR, 2.00; 95% CI, 1.33–3.01), and ICH (RR, 2.65; 95% CI, 1.83–3.82) were associated with a higher risk of developing PTE.

Subgroup analyses of clinical severity of TBI indicated that both MBI (RR, 2.36; 95% CI, 1.96–2.84) and SBI (RR, 8.37; 95% CI, 5.21–13.45) were associated with a higher risk of developing PTE, but the risk of developing PTE in patients with SBI was higher than that in patients with MBI (Table 2). The risk of developing PTE after skull fracture, MBI, and SBI peaked within the first year after TBI, and then gradually decreased. However, the risk of PTE was sustained at a high level for >10 years after skull fracture (RR, 2.06; 95% CI, 1.37–3.10), MBI (RR, 1.59; 95% CI, 1.35–1.87), and SBI (RR, 3.72; 95% CI, 2.13–6.50 (Fig. 3).

3.4. Publication bias and heterogeneity

Potential publication bias was assessed by visual inspection of funnel plots, and an asymmetric plot suggested risk of publication bias (Fig. S1). Substantial heterogeneity of effect estimates between studies was observed for gender, clinical findings, abnormal neuroimaging findings, clinical severity of TBI, and ASS. Sources of heterogeneity were identified in reviewed studies, and included differences in sample size, study design, method of ascertaining risk factors for PTE, and follow-up duration.

4. Discussion

Traumatic brain injury is the cause of epilepsy in almost 30% of subjects who develop epilepsy between ages 15 and 34 years [2,28]. Epilepsy that develops after TBI has several important features that make it distinct and particularly worthy of study. First, PTE is recognized as one of the most common forms of acquired epilepsies in young people [28], and it is strongly associated with poor functional outcomes and increased mortality [6]. Second, the increase in SBI associated with missile and blast injuries in modern warfare augments the necessity for further