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Full Length Article

Increased risk of venous thromboembolism in patients with brain tumors: A systematic review and meta-analysis

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ABSTRACT

Background: Currently published studies investigating the association between brain tumors and venous thromboembolism (VTE) risk have yielded inconsistent findings. To provide a more precise estimate for this association, we firstly performed a meta-analysis by pooling all currently available data.
Methods: Pooled relative risks (RRs) with 95% confidence intervals (95% CIs) were calculated by use of STATA 12.0 software. All eligible studies were identified by a comprehensive literature search in databases of PubMed, Embase, Web of Science, and Google scholar.
Results: According to the inclusion criteria, 9 independent studies were finally included into this study. Individuals with brain tumors were at an increased risk of VTE (RR = 1.66, 95% CI 1.31–2.12, $P < 0.001$), particularly those undergoing surgery (RR = 1.68, 95% CI 1.44–1.98, $P < 0.001$). Stratified analysis by type of tumor showed that the risk of VTE was significantly associated with glioma (RR = 1.68, 95% CI 1.44–1.98, $P < 0.001$), high-grade glioma (RR = 1.70, 95% CI 1.29–2.23, $P < 0.001$), and glioblastoma multiforme (RR = 1.74, 95% CI 1.43–2.12, $P < 0.001$).
Conclusions: The present meta-analysis suggests increased risk of VTE in patients with brain tumors, particularly those undergoing surgery.

1. Introduction

Brain tumors are common diseases worldwide, accounting for approximately 2% cancer-related death [1]. The incidence, response to therapy, and overall survival of brain tumors differ greatly by age at diagnosis and histological types of tumor [2]. With advances in prevention, early detection, and treatment of brain tumors, overall survival and prognosis of brain tumors have been improved over the past few decades [3]. Ionizing radiation is a well-established environmental risk factor for brain tumors [2,4]. Nonetheless, the molecular mechanisms of brain tumors remains poorly understood.

Cumulative incidence has implicated that the incidence of symptomatic VTE among glioma patients has been up to 36% during their treatment [5,6]. Patients with high-grade gliomas (HGGs) were reported to be at elevated risk of venous thromboembolism (VTE) [7,8]. In addition, the administration of chemotherapy can increase the risk of such venous thromboembolic complications.

VTE, including deep vein thrombosis (DVT) and pulmonary emboli (PE), is common in patients with brain tumors. It remains one of the leading causes of cancer-related deaths worldwide. A previous meta-analysis has shown that the relative risk of VTE was significantly increased for cancers of ovary, pancreas, liver, blood, brain, kidney, lung, colon, and esophagus [9], suggesting cancer patients are more likely to develop VTE. However, studies published from 2008 up to now, which investigated the association between brain tumors and the risk of VTE, were not included for the meta-analysis. Besides, the relative small sample size was limited to provide a sufficient statistical power for estimating this association. Furthermore, the risk of VTE was not discussed in relation to specific brain tumors, such as glioma and glioblastoma multiforme. The purpose of this meta-analysis was to determine the risk of VTE in brain tumor patients by pooling all currently available data. In addition, the association between brain tumors and VTE risk was estimated in consideration of tumor types and patients' surgical status. The present study is valuable for identifying novel clinical risk factors for VTE. The PRISMA checklist as a supplementary material has shown details of how the present meta-analysis fulfills the required criteria for conducting and reporting a systematic review and meta-analysis [10].

2. Materials and methods

2.1. Literature search

A comprehensive literature search was performed in PubMed, Embase, Web of Science, and Google scholar databases up to July 8, 2015 to identify eligible studies. The following terms were used to maximize the search specificity and sensitivity: brain tumor, glioma, high-

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grade gliomas, glioblastoma multiforme, deep venous thrombosis, pulmonary embolism, venous thromboembolism. The search algorithm used in PubMed was as following: (((((((glioblastoma multiforme) OR glioblastoma) OR gliomas) OR glioma) OR brain tumors) OR brain tumor)) AND (((venous thromboembolism) OR pulmonary embolism) OR deep venous thrombosis). We also checked relevant references of retrieved studies to identify additional articles. The literature search was independently carried out by two investigators.

2.2. Inclusion/exclusion criteria

Studies were potentially eligible for inclusion in this meta-analysis if they conformed to the following inclusion criteria: (a) observational studies investigating the association between brain tumors and the risk of VTE; (b) case–control or cohort studies; (c) presenting the odds ratios (ORs) or relative risks (RRs) or hazard ratios (HRs) and 95% confidence intervals (95% CIs) of VTE associated with brain tumors. The following studies were excluded: (a) reviews; (b) duplicated data; (c) studies did not provide ORs or RRs or HRs with 95% CIs. If data were duplicated in more than one study, the most recent or complete study was included into our study.

2.3. Data extraction

The following study characteristics were independently extracted by two investigators through a strict double-blind review process: name of first author, study design, sample size, publication year, ethnicity, study population, time of follow-up, available RRs or HRs or ORs with 95% CIs, adjustment factors, analysis strategy, and baseline characteristics including age, gender, and race, if available. Discrepancies on all extracted items were settled down by consensus.

2.4. Statistical analysis

The strength for the relationship between brain tumors and VTE risk was weighed by calculating the pooled relative risks (RRs) with 95% confidence intervals (95% CIs). Subgroup analyses by surgery status and type of tumor were also conducted. We performed heterogeneity analysis and selected available effect models based on the results. The pooled RRs with 95% CIs were calculated by Cochran's Q and I^2 statistic tests [11,12]. When the P value for Cochran's Q was less than 0.05 or the I^2 was more than 50%, there was statistically significant heterogeneity among those included studies. Fixed-effects model was applied in case of insignificant between-study heterogeneity [13]; otherwise, random-effects model was adopted if the heterogeneity was statistically significant [14]. Sensitivity analysis by sequentially omitting single studies was carried out for estimation. The risk of publication bias was evaluated by both Begg's funnel plot analysis and Egger's test [15,16]. The Trim and Fill method was also used to estimate the publication bias risk in this study [17]. All P values were two-sided. The STATA 12.0 software was used for all statistical analysis (StataCorp, College Station, TX, USA).

3. Results

3.1. Literature search results and characteristics of all included studies

After a comprehensive literature search in PubMed, Embase, Web of Science, and Google scholar databases, 70 studies were retrieved. After checking titles and abstracts, 39 studies not estimating the association between brain tumors and VTE risk, 10 not associated with the risk of VTE, 9 reviews, and one about the risk of cancer were all excluded. After reading full texts of the last 11 studies, 2 were excluded due to unavailable data. Finally, 9 eligible studies were included into the current meta-analysis [18–26]. The detailed flowchart for literature inclusion was presented in Fig. 1. Table 1 showed the baseline characteristics of all included studies. Among the 9 studies, 8 were conducted among Caucasians [18–23,25,26], while only one among a mixed population [24]. Patients with brain tumors from 7 studies had undergone surgical treatments [18,20,22–26], while the surgery status of all cases from the other 2 individual studies was not reported detailedly [19,21]. The risk of VTE was primarily investigated related to glioma, HGG and glioblastoma multiforme.

3.2. Association between brain tumors and VTE risk

Overall, the pooled RR under random-effects model revealed that individuals with brain tumors were at a significantly increased risk of VTE (RR = 1.66, 95% CI 1.31–2.12, $P < 0.001$) (Table 2, Fig. 2). However, the heterogeneity analysis showed obvious heterogeneity between total included studies ($I^2 = 63.7\%$, $P = 0.005$) (Table 2). Sensitivity analysis did not materially change this significant association (Fig. 3).

3.3. Stratified analysis by surgery status

According to the status of all brain tumor patients, patients undergoing surgical treatments were more susceptible to VTE (RR = 1.68, 95% CI 1.44–1.98, $P < 0.001$) (Table 2). In addition, the between-study heterogeneity was not significant in this stratified analysis. The source of between-study heterogeneity was mainly attributed to studies not presenting detailed information for the status of those patients with brain tumors (Table 2).

3.4. Stratified analysis by types of tumor

The stratified analysis by types of tumor showed that increased risk of VTE was significantly associated with glioma (RR = 1.68, 95% CI 1.44–1.98, $P < 0.001$), high-grade glioma (RR = 1.70, 95% CI 1.29–2.23, $P < 0.001$), and glioblastoma multiforme (RR = 1.74, 95% CI 1.43–2.12, $P < 0.001$), respectively (Table 2). No significant between-study heterogeneity was observed in this stratified analysis.

3.5. Publication bias

As shown in Fig. 4, Begg's funnel plot for overall analysis was symmetrical. The P value for Begg's test was 0.53, which showed there was low risk of publication bias. However, the P value for Egger's test was 0.03, which suggested possible risk of publication bias. When using Trim and Fill method, two possibly "missing" studies were added, but individuals with brain tumors were still at a significantly increased risk of VTE (RR = 1.52, 95% CI 1.18–1.95, $P < 0.001$) (Fig. 5).

4. Discussion

VTE is a frequent and potentially fatal health problem, which has become a well documented complication of cancer. The coagulation system of cancer patients is activated and is further amplified by treatment with chemotherapy, radiation or surgery [27]. It has been well demonstrated that patients with cancer are at 4–20 fold increased risk of VTE, while the risk is further increased by chemotherapy [28,29]. The significant relationship between clotting activation and cancer supports the view that malignancy itself is a hypercoagulable state, thus VTE in tumor neurosurgery is common even with VTE prophylaxis [27,30,31]. A hypercoagulable state in malignancies holds implications for the development of VTE and poor clinical outcomes, including brain tumors [9,32]. The association of brain tumors and risk of VTE has drawn much attention for the past few years. To the best of our knowledge, chronic activation of the coagulation system is in particular frequent in brain tumors, where vasoocclusive thrombosis in tumors may lead to hypoxia, necrosis, and angiogenesis. Enhanced emission of circulating procoagulants often appears when spontaneous or iatrogenic bleeding occurs in brain tumors [33,34]. As a result, brain tumor