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Biomarkers related with seizure risk in glioma patients: A systematic review

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ABSTRACT

Increasing evidence indicates that genetic biomarkers play important roles in the development of glioma-associated seizures. Thus, we performed a systematic review to summarise biomarkers that are associated with seizures in glioma patients. An electronic literature search of public databases (PubMed, Embase and Medline) was performed using the keywords glioma, seizure and epilepsy. A totall of 26 eligible studies with 2224 cases were included in this systematic review of publications to 20 June, 2016. Genetic biomarkers such as isocitrate dehydrogenase 1 (IDH1) mutations, low expression of excitatory amino acid transporter 2 (EAAT2), high xCT expression, overexpression of adenosine kinase (ADK) and low expression of very large G-protein-coupled receptor-1 (VLGR1) are primarily involved in synaptic transmission, whereas BRAF mutations, epidermal growth factor receptor (EGFR) amplification, miR-196b expression and low ki-67 expression are associated with regulation of cell proliferation. However, there is limited evidence regarding the roles of RAD50 interactor 1 (RINT1) and olig2 in epileptogenesis among glioma patients. Glioma-related seizure was related to the dysfunction of tumor microenvironment. Our findings may provide new mechanistic insights into targeted therapy for glioma-related seizures and may result in the development of multi-target therapies.

Contents

1. Introduction

Seizures are common symptoms in patients with glioma and whereas 46%–90% of patients with grade II glioma reportedly experience epileptic seizures before surgery, 42%–71% and 29%–52% of grade III and IV glioma patients, respectively, experience seizures [1–11]. Moreover, the incidence of seizures reportedly depends on

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tumour grade and type [12,13] and increased risks of seizure have been observed in patients with gliomas in regions of the temporal lobe [14]. Although glioma-related seizures have favourable effects on the overall survival of glioma patients [15–17], undesirable influences on quality of life quality, cognitive dissonance and significant morbidity are inevitable [18], especially long-term epilepsy associated tumor(LEAT) which more commonly encountered in surgical series of patients who have been investigated and treated for drug-resistant seizure episodes for 2 years or longer [19]. Thus, better understanding of the pathogenic mechanisms of glioma-related seizures may contribute to seizure control and improve quality of life. It is accepted that these mechanisms of tumour-associated seizures are anfractuous and include multiple factors, such as disturbances of metabolism in peritumour microenvironments, mass effects, alterations of genetic biomarkers, turbulence of the blood brain barrier and abnormal expression of ion channels [3,20,21]. Recent studies of biomarkers associated with epilepsy have resulted in several reports of genetic biomarkers that play a role in the aetiology of seizures, including isocitrate dehydrogenase 1 (IDH1) mutations, RAD50 interactor 1 (RINT1) expression and adenosine kinase (ADK) overexpression [22–24]. Moreover, associations of genetic biomarkers with the development of seizures in glioma patients are increasingly demonstrated. However, most of these studies validate single biomarkers and have inconsistent results. Thus, we performed a system review to summarise current biomarkers associated with seizures in glioma patients and comprehensively reviewed the literature to inform future studies of targeted therapy for seizure control.

2. Methods and materials

2.1. Search strategy and selection criteria

We performed systematic literature searches in PubMed and Embase until Jun 2016 using the keywords glioma, seizure and epilepsy according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. Included studies met the following criteria: 1) diagnosis of glioma based on World Health Organization (WHO) grade, 2) evaluation of the relationship between at least 1 biomarker and glioma-associated seizures, 3) written in English. Exclusion criteria were as follows: 1) review, 2) case reports, 3) only symptomatic seizures described. Reference lists of included studies were searched to identify further eligible studies. Two researchers (Zhou Xingwang and Dong Hui) extracted the following data from the included studies using a standard form: The surname of the first author, the names of genetic biomarkers, the year of publication, geographical location, ethnicity of cases, sample size, tumour grade and the relationship between biomarkers and glioma-associated seizure.

3. Results

Initially, 1699 unique records were retrieved from bibliographic databases, and of these, 168 full text articles were assessed further for eligibility. Finally, after exclusion had been applied, 26 eligible studies with a total of 2224 cases were included (Fig. 1). Years of publication of these articles ranged from 2007 to 2015 and sample sizes ranged from 9 to 492. Eighteen studies included Caucasian patients and eight studies were of Asian patients. Ten studies included patients with WHO grade II glioma, three studies reported WHO IV grade gliomas, four reported WHO grades I–IV gliomas and three reported WHO grade I, three included WHO grades II–IV, two studies showed WHO grades I and II gliomas and one study reported data from patients with grade III gliomas (Table 1). After review of included full text articles, eligible studies were categorised as follows: (1) genetic biomarkers associated with synaptic transmission; (2) genetic biomarkers associated with the regulation of cell proliferation;(3) genetic biomarkers associated with inflammation;(4) unknown pathomechanisms of biomarkers in the aetiology of glioma-related seizure.

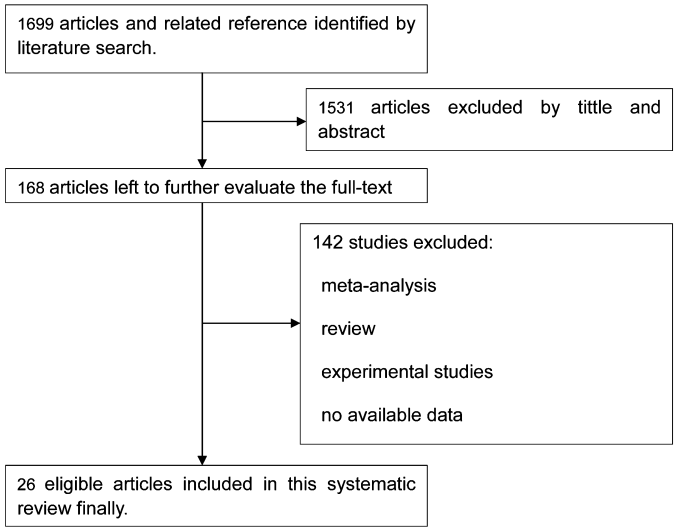

Fig. 1. The procedure of literature search and selection.

3.1. Genetic biomarkers associated with synaptic transmission

Twenty two studies of synaptic transmission were included and contained evaluations of over 20 associated biomarkers [3,23,26–32]. Among these studies, eight assessed associations of IDH1/2 and glioma-related seizures but inconsistent conclusions are reported [23,26–32]. Specifically, whereas two studies reported negative associations between IDH1 and seizures in patients with WHO II grade gliomas [27,28] and one study showed consistent data in WHO III glioma patients [29], no p values, odds ratios (OR) or 95% confidence intervals (95% CI) were reported. Five studies suggested that IDH1 played a role in the development of glioma patients with seizure [23,26,30–32], and Florian et al. [26] concluded that seizures were associated with IDH1 or IDH2 mutations in 79 WHO grade II glioma patients (OR, 22.563; 95% CI, 3.147161–745). Moreover, in a retrospective study by Liang et al. [30] mutation of IDH1 was the strongest predictor of preoperative seizure (OR, 6.130; 95% CI, 1.523–24.669). Furthermore, Liubinas et al. [31] indicated that the percentage of cells that were positive for the IDH1-R132H mutation was higher in low grade glioma patients with seizure than in those without seizures (median, interquartile range (IQR) 25.3%, 8.6–53.5% vs. 5.2%, 0.6–13.4%, p = 0.03), and Zhong et al. [23] and Skardelly et al. [32] showed corresponding odds ratios (OR, 1.902; 95% CI, 1.026–3.526; OR, 2.52; 95% CI, 1.12–5.81, respectively). All of these studies suggest that IDH1 mutations result in activation of *N*-methyl-D-aspartate (NMDA) receptors and accumulation of 2-hydroxyglutarate (2HG), which is structurally similar to glutamate.

Dysfunction of glutamate receptors signaling, or glutamate process and elevation of extracellular glutamate were suggested to be associated with the development of seizure [33]. Yuen et al. [3] explored the influence of excitatory amino acid transporters (EAAT) and system Xc (SXC), which is a brain cysteine/glutamate exchange complex, and suggested relationships between lower glutamate concentrations and EAAT2 expression (r = −0.27; 95% CI, 0.48–0.04; p = 0.02) and higher log glutamate concentrations and expression of a SXC catalytic subunit, xCT (r = 0.30, 95% CI 0.07–0.50, p = 0.01). They also demonstrated low EAAT2 expression, high xCT