Review Article
Association between interleukin-1β and epilepsy or children’s febrile seizures: a meta-analysis

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Abstract: Objective: While interleukin-1β (IL-1β) could influence the development of various diseases of the central nervous system, the conclusions are controversial in epilepsy and children’s febrile seizures. A meta-analysis was conducted to investigate the correlation between IL-1β with epilepsy or children’s febrile seizures. Methods: Pertinent studies on IL-1β and epilepsy or seizure were identified by retrieval of PubMed, EMBASE, Web of Science and EBSCO databases till June, 2016. The standard mean difference (SMD) and corresponding 95% confidence interval (CI) were to evaluate the strength of association. Results: 11 studies with a total of 247 patients and 615 controls were included in this meta-analysis. The results demonstrated that there was no difference in IL-1β level between two groups. The SMD was 0.21 (95% CI: -0.15 to 0.57, random effect model). In subgroup analysis, results were similar in child versus adult and epilepsy versus febrile seizures, with SMD 0.24 (95% CI: -0.24 to 0.72) versus 0.18 (95% CI: -0.46 to 0.82), 0.15 (95% CI: -0.37 to 0.67) versus 0.29 (95% CI: -0.27 to 0.84), respectively. In addition, among these studies, 6 evaluated the correlation between IL-6 and epilepsy and children’s febrile seizures, and the result demonstrated that higher level of IL-6 was found in these patients, the SMD were 0.68 (95% CI: 0.28-1.07, random effect model). No significant publication bias was found in the studies. Conclusions: No significance of IL-1β is found between epilepsy and febrile seizures patients and controls. However, more well-designed studies still need to be performed in the future.

Keywords: IL-1β, epilepsy, febrile seizures, children, meta-analysis

Introduction

Epilepsy (EP) is a nervous system disorder that affects ~50 million people worldwide and is characterized by an enduring predisposition to generate seizures [1]. There is a growing body of evidence supporting the hypothesis that inflammatory cytokines act as disease-modifying molecules and are involved in the pathogenesis and the development of EP seizures [2-5]. Another type of seizure known as a febrile seizure (FS) is the most common seizure in children, with a prevalence of 2-5% [6]. Complex interactions between immune-inflammatory process and cytokine activation are also involved in febrile seizures pathogenesis [7]. Interleukin-1 (IL-1) plays an important role in inflammation, which often gives rise to tissue destruction. Among different inflammatory cytokines studied such as tumor necrosis factor-a (TNF-a) and IL-17A, IL-6, IL-1β and interleukin-1 receptor antagonist (IL-1Ra) have attracted most attention in clinical studies [8-10]. According to current published studies, the association of IL-1β with EP and FS is controversial. Some researchers suggest that there is an increase in IL-1β in epilepsy patients [11, 12], in Pernot’s study, they found that IL-1b, IL-1Ra, and COX-2 mRNA were specifically increased during initial status epilepticus with a different time course in the ipsilateral hippocampus [12], whereas other studies demonstrate no obvious change [13, 14]. Postictal plasma levels of IL-1RA and IL-1β did not significantly differ from baseline in the patients with epilepsy in Alapirtti’s research, although IL-1β did not show a change during the seizure in plasma in the study, the thought has been given that it’s possible that IL-1β is produced in low quantities locally in the brain and has a role in seizures [13]. Therefore, we performed this meta-analysis of published studies to investigate the integrated effect sizes of IL-1β levels in EP and FS.
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Materials and methods

Search strategy

A number of databases including PubMed, EMBASE, Web of Science and EBSCO were electronically searched for eligible studies assessing the association between IL-1β and EP or FS for all literature published until June 2016. The following search criteria were used: “interleukin-1 beta” OR “IL-1β” AND “epilepsy” OR “febrile seizures” OR “febrile convulsion” OR “seizure”. There were no restrictions on regions, sample size, or type of report so as to minimize potential publication bias. The reference lists of retrieved articles were analyzed to identify additional relevant studies.

Inclusion and exclusion criteria

All studies reported IL-1β level between two groups, and therefore the results are presented as pooled SMDs. Meta-analyses, letters, reviews, and editorial articles were excluded.

Data extraction

Two reviewers independently searched and selected literature and extracted relevant data. Disagreements were resolved by a third investigator. The extracted data included: the first author, year of publication, country of origin, course of disease, diagnostic classification, sample size, sample source, etc.

Statistical analysis

We used SMD and 95% CI to assess the association between IL-1β and EP or FS. Heterogeneity among included studies was examined by chi-square-based Q test and I² test. If the data showed no heterogeneity (P>0.10, I²<50%), the Mantel-Haenszel fixed effect model was used, otherwise the DerSimonian-Laird random effect model was applied. Publication bias was quantitatively assessed by Egger’s linear regression test and visual inspection of Begg’s funnel plots. Data were analyzed using STATA 11.0 SE software (Stata Statistical Software, College Station, TX, USA, www.stata.com).

Results

Outcomes

The primary clinical endpoint was IL-1β levels in either the EP or FS group or a control group. Secondary outcomes were levels of other cytokines, including IL-6, IL-1 receptor antagonist (IL-1Ra), and tumor necrosis factor alpha (TNF-a) in plasma or cerebral spinal fluid (CSF).

Quality assessment

The quality of studies was examined and controlled in accordance with checklists of Meta-analysis of Observational Studies in Epidemiology (MOOSE) [15].

Figure 1. Flow chart of study selection.

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Electronic database searches identified 326 studies with possible relevance to our investigation. Further investigation led to the exclusion of 267 of these studies due to non-relevance. 38 articles were further excluded due to duplication or not being associated with IL-1β. The full texts of the remaining 21 articles were read by two independent investigators. From these 21 articles, 10 articles were excluded because of no primary outcome. The remaining 11 articles [16-26], which comprised 247 patients and 615 controls, met all inclusion cri-
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Table 1. Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Age (P/C) years</th>
<th>Course of disease (years)</th>
<th>Sample source</th>
<th>Diagnostic classification</th>
<th>Sample size (P/C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lahat 1997</td>
<td>Israel</td>
<td>0.7-2.3</td>
<td>Unclear</td>
<td>Plasma</td>
<td>Febrile seizures</td>
<td>10/10</td>
</tr>
<tr>
<td>Peltola 2000</td>
<td>Finland</td>
<td>15-60</td>
<td>Unclear</td>
<td>CSF/plasma</td>
<td>Clonic seizures</td>
<td>12/18</td>
</tr>
<tr>
<td>Straussberg 2001</td>
<td>Israel</td>
<td>0.55-4</td>
<td>Unclear</td>
<td>Plasma</td>
<td>Febrile convulsions</td>
<td>13/11</td>
</tr>
<tr>
<td>Haspolat 2002</td>
<td>Turkey</td>
<td>0.6-5</td>
<td>Unclear</td>
<td>CSF/plasma</td>
<td>Febrile seizures</td>
<td>29/15</td>
</tr>
<tr>
<td>Hulkkonen 2004</td>
<td>Finland</td>
<td>22-65</td>
<td>17-63</td>
<td>Plasma</td>
<td>TLE, FLE</td>
<td>10/400</td>
</tr>
<tr>
<td>Tomoum 2007</td>
<td>Egypt</td>
<td>0.5-5</td>
<td>Unclear</td>
<td>Plasma</td>
<td>Simple, complex</td>
<td>33/38</td>
</tr>
<tr>
<td>Behmanesh 2012</td>
<td>Iran</td>
<td>1.82 (0.3)</td>
<td>Unclear</td>
<td>Plasma</td>
<td>Febrile convulsion</td>
<td>30/30</td>
</tr>
<tr>
<td>Youn 2012</td>
<td>Korea</td>
<td>Newborns</td>
<td>22.1 (19.4)</td>
<td>Plasma</td>
<td>GTC, subtle</td>
<td>13/15</td>
</tr>
<tr>
<td>Tombini 2013</td>
<td>Italy</td>
<td>51.3 (18.8)</td>
<td>47.3 (19.9)</td>
<td>Plasma</td>
<td>TLE, XLE</td>
<td>37/43</td>
</tr>
<tr>
<td>Uludag 2015</td>
<td>Turkey</td>
<td>19-59</td>
<td>22-53</td>
<td>Plasma</td>
<td>TLE, XLE</td>
<td>38/20</td>
</tr>
<tr>
<td>Ishikawa 2015</td>
<td>Japan</td>
<td>4.54 (2.63)</td>
<td>5.49 (3.61)</td>
<td>Plasma</td>
<td>Daily seizure</td>
<td>12/15</td>
</tr>
</tbody>
</table>

Abbreviations: P/C: patient group/control group; CSF: cerebral spinal fluid; FLE: frontal lobe epilepsy; TLE: temporal lobe epilepsy; extra-temporal lobe epilepsy (XLE); idiopathic generalized epilepsy (IGE); GTC, generalized tonic-clonic.

Figure 2. Forest plot between IL-1β with epilepsy and febrile seizures, with subgroups of child and adult.

Study characteristics

The characteristics of the included studies are given in Table 1. Among these studies, 2 were conducted in Israel, 2 in Finland, 2 in Turkey, 1 in Italy, 1 in Japan, 1 in Iran, 1 in Korea and 1 in Egypt. The sample source was either plasma or CSF. Diagnostic classification details are also given in Table 1. The quality of included studies was generally good, with results of study quality assessment yielding a score of 6 or above for all included studies.

Association between IL-1β and EP or FS

Eleven studies with a total of 247 patients and 615 controls were included in this meta-analysis. Meta-analysis demonstrated that there was no difference between the two groups when samples were from plasma (Figures 2 and 3). The SMD was 0.21 (95% CI: -0.15 to 0.57, random effect model, I^2>50%). In subgroup analysis, results were described as figures in child versus adult and EP versus FS, with a SMD of 0.24 (95% CI: -0.24 to 0.72) versus 0.18 (95% CI: -0.46 to 0.82) and 0.15 (95% CI: -0.37 to 0.67) versus 0.29 (95% CI: -0.27 to 0.84), respectively.

Association between IL-1Ra and EP or FS

Five studies evaluated the correlation between IL-1Ra and EP or FS. Meta-analysis results demonstrated no difference between cases and controls, with a combined SMD of -0.12 (95% CI: -1.21 to 0.97). Subgroup analysis showed that the SMDs were -0.1 (95% CI: -1.44 to 1.25, random effect model) and -0.22 (95% CI: -0.96 to 0.53) (Figure 4).
Interleukin-1β with epilepsy and febrile seizures

Cytokines not only participate in the regulation of immunity, they can also regulate the function of neurons and glia and affect the function of synapses. Though inflammatory markers have been implicated in the pathophysiology of seizures and epilepsy [4, 5, 9], IL-1β is upregulated after experimental animal seizures, but in clinical studies there have not always been observable differences in IL-1β concentrations after the seizures. Our analyses also did not reveal an association with IL-1β, which may indicate it has no direct effect on EP or FS. This is most possibly explained by the researches that the increased expression of IL-1β is observed mainly in the hippocampal area which does not have any effect on the levels of soluble cytokines either in the cerebrospinal fluid or blood circulation.

An EP model demonstrates that induced seizures can lead to an increase of IL-1β transcription in different regions [27]. Some experiment suggests that stimulation of the convulsions drugs and excitatory toxin can promote hippocampal microglia produce IL-1β, and exogenous IL-1β could extend abnormal discharge time, resulting in increased epilepsy activity, while IL-1Ra can play a role of strong anticonvulsants [28]. The above data indicate that IL-1β may participate in the function of neurons damage.

Discussion

The current meta-analysis was performed to investigate the association of IL-1β with epilepsy (EP) or febrile seizures (FS). Data from 11 clinical studies was pooled and analyzed. Our analyses did not identify significant differences in levels of IL-1β between cases and controls. However, higher levels of IL-6 were found in cases. To our knowledge, this is the first meta-analysis examining the relationship between cytokines and EP or children’s FS.

Association between IL-6 and EP or FS

Six studies evaluated levels of IL-6 and meta-analysis revealed a significant difference between the case and control groups (Figures 5 and 6). The SMD was 0.68 (95% CI: 0.28 to 1.07, random effect model, I²>50%). In sub-group analyses, results were described as figures in adult versus child and EP versus FS, with a SMD of 0.77 (95% CI: 0.49 to 1.05) versus 0.45 (95% CI: -1.3 to 2.2) and 0.83 (95% CI: 0.57 to 1.09) versus -0.43 (95% CI: -1.18 to 0.32), respectively.

Association between TNF-a and EP or FS

Four studies analyzed TNF-a levels in cases and controls and meta-analysis revealed a combined SMD of -0.36 (95% CI: -0.83 to 0.12). There was no significant difference in children for either the EP or FS subgroups, whereas, in the adult subgroups, the SMD was -0.66 (95% CI: -1.18 to -0.14). Finally, 3 studies had the record of IL-1β in CSF, no difference was found between two groups as well as subgroups.

Publication bias

No significant publication bias was observed. Visual inspection of Beggs’s funnel plot showed substantial asymmetry (Figure 7). The Beggs’s rank correlation test indicated no evidence of publication bias among studies (P=0.187).
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Figure 4. Forest plot between IL-1Ra with epilepsy and febrile seizures.

Figure 5. Forest plot between IL-6 with epilepsy and febrile seizures, with subgroups of adult and child.
One study found that IL-1β levels increased significantly in CSF with febrile convulsions, while the levels of peripheral blood IL-1β showed no significant change [29]. Other research indicated that the level of IL-1β had no significant correlation with the number of febrile seizures, fever, and convulsion duration [21]. The results show that IL-1β may act as pyrexin, causing high fever and convulsions.

When compared with wild type mice, IL-6 knockout mice are more susceptible to seizures [30]. One study also found a strong association between temporal lobe epilepsy and the overproduction of IL-6 [31]. There is a clear correlation between cerebrospinal fluid and plasma concentrations of this cytokine, and plasma levels of IL-6 are most likely originated in the central nervous system via venous drainage. Our meta-analysis also revealed an association of high IL-6 levels and EP.

However, as cytokines, its role in promoting convulsion and anticonvulsive often depends on their concentration, duration and interact...
with other inflammatory factor of composite effect. So somehow we did not find other associations with epilepsy or children's febrile seizures.

The meta-analysis presented here had certain limitations. Heterogeneity was high, so a random effect model was used. The source of heterogeneity may have come from studies being conducted in different countries, study population age, course of disease, etc. Also, only included English-language literature was included so publication bias may exist.

In conclusion, based on our results of pooled analysis, the IL-1β level in epilepsy and febrile seizures patients is not increasing significantly compared with the control group. However, IL-6 level has risen conspicuously in the patient group. Further studies and more clinical data will be needed to increase our understanding of the possible role of cytokines EP or FS.

Disclosure of conflict of interest

None.

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