Int J Clin Exp Med 2017;10(5):7367-7374
www.ijcem.com /ISSN:1940-5901/IJCEM0048118

Review Article

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

Wenbo Li, Yaohui Zhang, Yuqing He, Peng Yan, Liping Wei

Department of Neurology, Luoyang Central Hospital Affiliated to Zhengzhou University, Henan Province, China

Received November 29, 2016; Accepted March 26, 2017; Epub May 15, 2017; Published May 30, 2017

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.

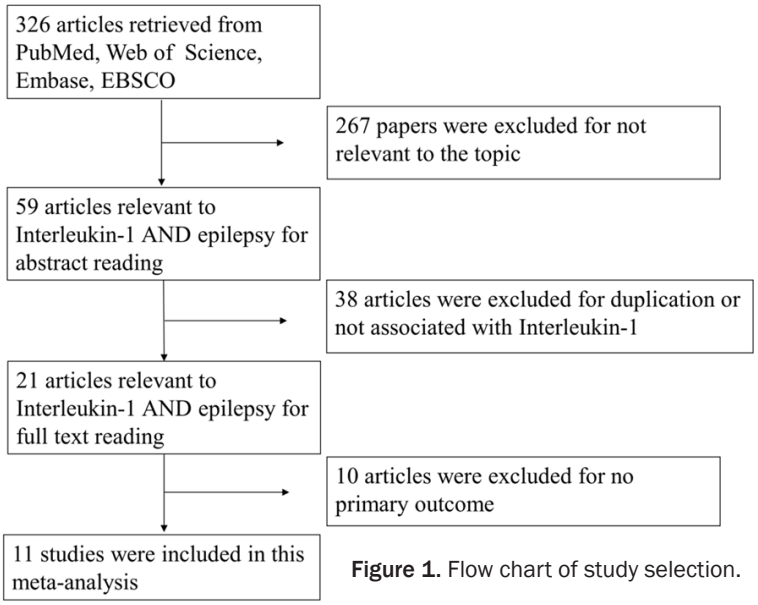

Figure 1. Flow chart of study selection.

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].

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 I^2 test. If the data showed no heterogeneity ($P>0.10$, $I^2<50\%$), the Mantel-Haenszel fixed effect model was used, otherwise the DerSimonian-Laird random effect model was applied. Pu-blication 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

Literature search

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-

Table 1. Characteristics of studies included in the meta-analysis

Study	Country	Age (P/C) years		Course of disease (years)	Sample source	Diagnostic classification	Sample size (P/C)
Lahat 1997	Israel	0.7-2.3	0.7-2.3	Unclear	Plasma	Febrile seizures	10/10
Peltola 2000	Finland	15-60	16-56	Unclear	CSF/plasma	Clonic seizures	22/18
Straussberg 2001	Israel	0.55-4	0.55-4	Unclear	Plasma	Febrile convulsions	13/11
Haspolat 2002	Turkey	0.6-5	0.6-5	Unclear	CSF/plasma	Febrile seizures	29/15
Hulkkonen 2004	Finland	22-65	18-60	17-63	Plasma	TLE, FLE	10/400
Tomoum 2007	Egypt	0.5-5	0.5-5	Unclear	Plasma	Simple, complex	33/38
Behmanesh 2012	Iran	1.82 (0.3)	1.82 (0.23)	Unclear	Plasma	Febrile convulsion	30/30
Youn 2012	Korea	Newborns	Newborns	Unclear	Plasma	GTC, subtle	13/15
Tombini 2013	Italy	51.3 (18.8)	47.3 (19.9)	22.1 (19.4)	Plasma	TLE, XLE	37/43
Uludag 2015	Turkey	19-59	22-53	2-47	Plasma	TLE, XLE	38/20
Ishikawa 2015	Japan	4.54 (2.63)	5.49 (3.61)	3.86 (2.48)	Plasma	Daily seizure	12/15

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.

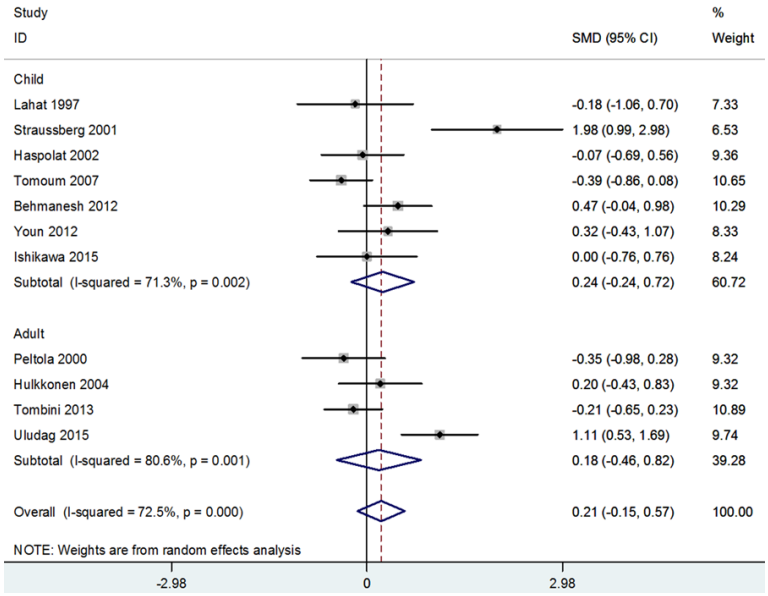

Figure 2. Forest plot between IL-1β with epilepsy and febrile seizures, with subgroups of child and adult.

teria and were included in the meta-analysis. The screening process is illustrated in **Figure 1**.

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**).

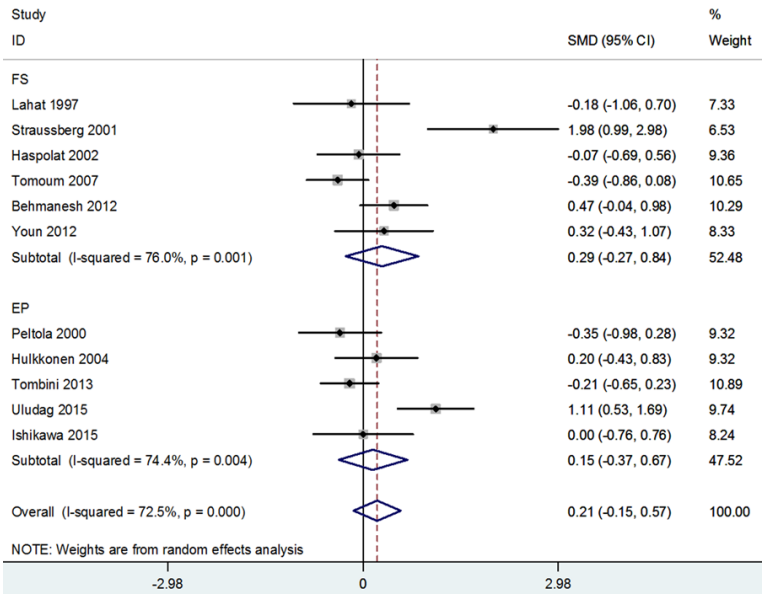

Figure 3. Forest plot between IL-1β with epilepsy and febrile seizures, with subgroups of febrile seizures and epilepsy.

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, I^2>50%). In subgroup 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 Begg's funnel plot showed substantial asymmetry (**Figure 7**). The Begg's rank correlation test indicated no evidence of publication bias among studies (P=0.187).

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.

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.

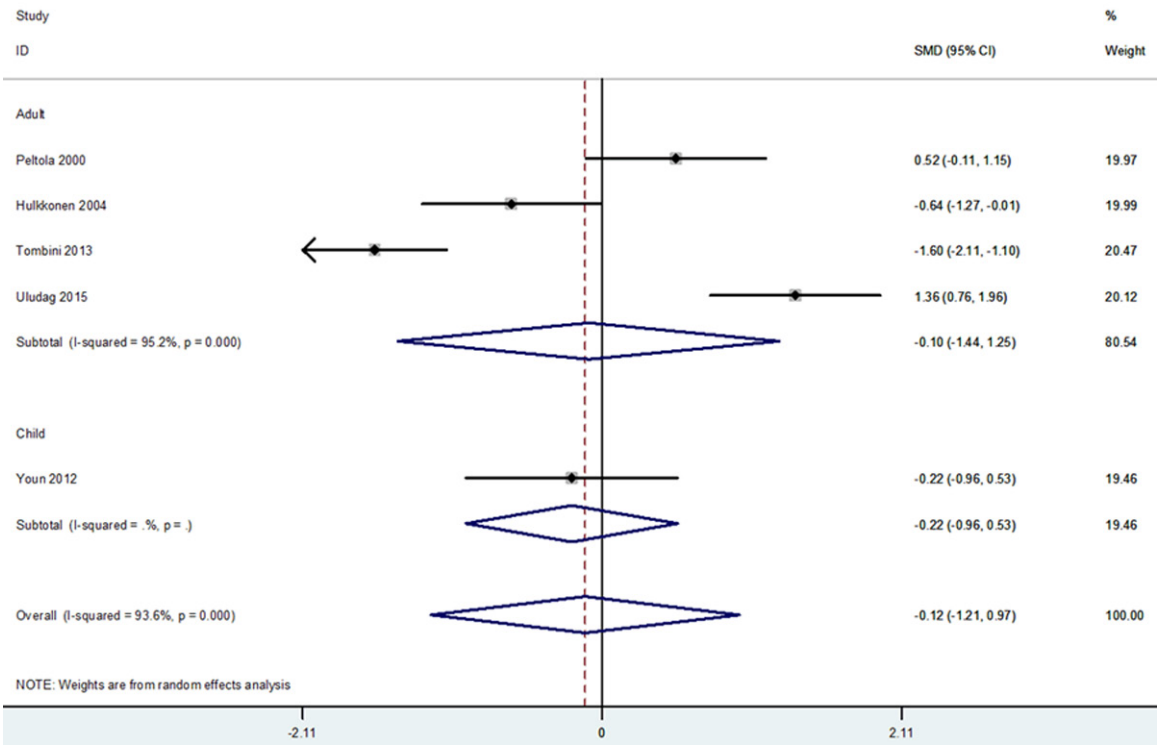

Figure 4. Forest plot between IL-1Ra with epilepsy and febrile seizures.

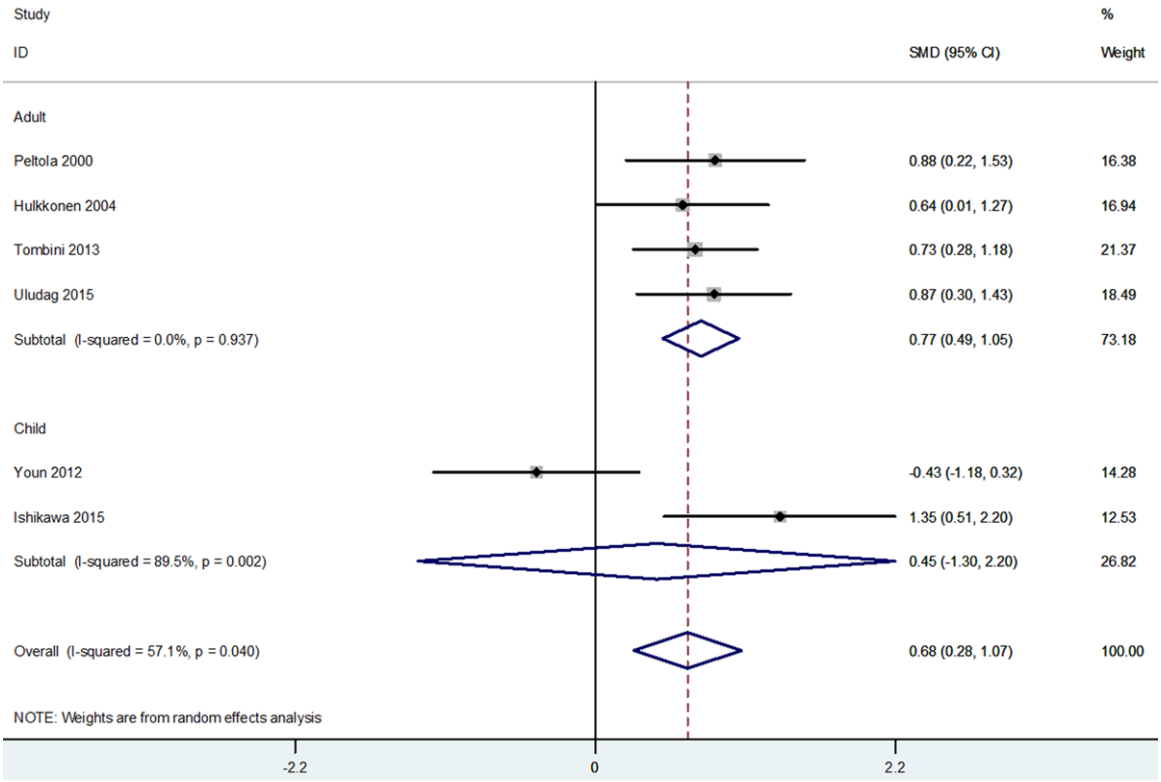

Figure 5. Forest plot between IL-6 with epilepsy and febrile seizures, with subgroups of adult and child.

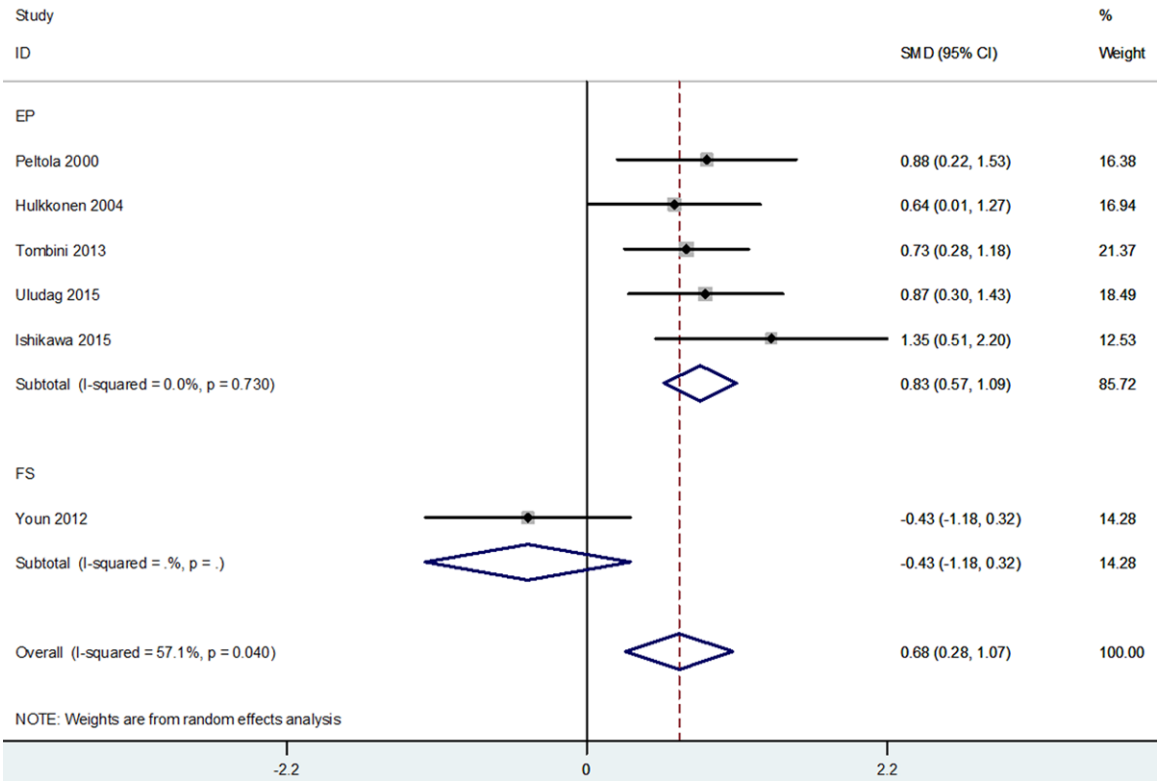

Figure 6. Forest plot between IL-6 with epilepsy and febrile seizures, with subgroups of epilepsy and febrile seizures.

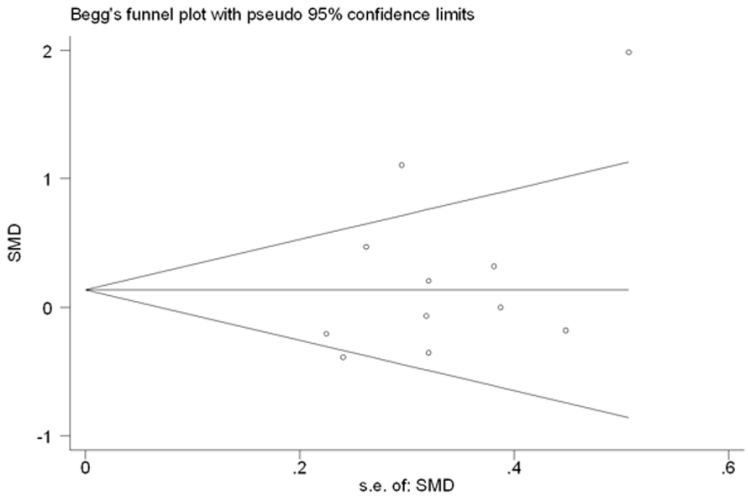

Figure 7. Begg's funnel plot of potential publication bias among included studies.

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.

Address correspondence to: Liping Wei, Department of Neurology, Luoyang Central Hospital Affiliated to Zhengzhou University, No. 288 Middle Zhongzhou Road, LuoYang 471000, Henan Province, China. Tel: +86-0379-63892249; Fax: +86-0379-63892249; E-mail: weiliping1122@163.com

References

[1] Duncan JS, Sander JW, Sisodiya SM and Walker MC. Adult epilepsy. Lancet 2006; 367: 1087-1100.

[2] Jankowsky JL and Patterson PH. The role of cytokines and growth factors in seizures and their sequelae. Prog Neurobiol 2001; 63: 125-149.

[3] Peltola J, Eriksson K and Keränen T. Cytokines and seizures. Arch Neurol 2001; 58: 1168-1169.

[4] Riazi K, Galic MA and Pittman QJ. Contributions of peripheral inflammation to seizure susceptibility: cytokines and brain excitability. Epilepsy Res 2010; 89: 34-42.

[5] Vezzani A, French J, Bartfai T and Baram TZ. The role of inflammation in epilepsy. Nat Rev Neurol 2011; 7: 31-40.

[6] Serdaroğlu G, Alpman A, Tosun A, Pehlıvan S, Özkınay F, Tekgül H and Gökben S. Febrile seizures: interleukin 1β and interleukin-1 receptor antagonist polymorphisms. Pediatr Neurol 2009; 40: 113-116.

[7] Tsai FJ, Chou IC, Hsieh YY, Lee CC, Lin CC and Tsai CH. Interleukin-4 intron 3 polymorphism is not related to susceptibility to febrile seizures. Pediatr Neurol 2002; 27: 271-274.

[8] Vezzani A and Granata T. Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia 2005; 46: 1724-1743.

[9] Vezzani A, Balosso S and Ravizza T. The role of cytokines in the pathophysiology of epilepsy. Brain Behav Immun 2008; 22: 797-803.

[10] Uludag IF, Bilgin S, Zorlu Y, Tuna G and Kirkali G. Interleukin-6, interleukin-1 beta and interleukin-1 receptor antagonist levels in epileptic seizures. Seizure 2013; 22: 457-461.

[11] Sinha S, Patil S, Jayalekshmy V and Satishchandra P. Do cytokines have any role in epilepsy? Epilepsy Res 2008; 82: 171-176.

[12] Pernot F, Heinrich C, Barbier L, Peinnequin A, Carpentier P, Dhote F, Baille V, Beaup C, Depaulis A and Dorandeu F. Inflammatory changes during epileptogenesis and spontaneous seizures in a mouse model of mesiotemporal lobe epilepsy. Epilepsia 2011; 52: 2315-2325.

[13] Alapirtti T, Rinta S, Hulkkonen J, Mäkinen R, Keränen T and Peltola J. Interleukin-6, interleukin-1 receptor antagonist and interleukin-1beta production in patients with focal epilepsy: a video-EEG study. J Neur Sci 2009; 280: 94-97.

[14] Lehtimäki K, Keränen T, Palmio J, Mäkinen R, Hurme M, Honkaniemi J and Peltola J. Increased plasma levels of cytokines after seizures in localization-related epilepsy. Acta Neurol Scand 2007; 116: 226-230.

[15] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA and Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000; 283: 2008-2012.

[16] Lahat E, Livne M, Barr J and Katz Y. Interleukin-1β levels in serum and cerebrospinal fluid of children with febrile seizures. Pediatr Neurol 1997; 17: 34-36.

[17] Peltola J, Palmio J, Korhonen L, Suhonen J, Miettinen A, Hurme M, Lindholm D and Keränen T. Interleukin-6 and interleukin-1 receptor antagonist in cerebrospinal fluid from patients with recent tonic-clonic seizures. Epilepsy Res 2000; 41: 205-211.

[18] Straussberg R, Amir J, Harel L, Punsky I and Bessler H. Pro-and anti-inflammatory cytokines in children with febrile convulsions. Pediatr Neurol 2001; 24: 49-53.

[19] Haspolat S, Mihçi E, Coşkun M, Gümüslü S, Özbenm T and Yegin O. Interleukin-1β, tumor necrosis factor-α, and nitrite levels in febrile seizures. J Child Neurol 2002; 17: 749-751.

[20] Hulkkonen J, Koskikallio E, Rainesalo S, Keränen T, Hurme M and Peltola J. The balance of inhibitory and excitatory cytokines is differently regulated in vivo and in vitro among therapy

resistant epilepsy patients. Epilepsy Res 2004; 59: 199-205.
[21] Tomoum HY, Badawy NM, Mostafa AA and Harb MY. Plasma interleukin-1β levels in children with febrile seizures. J Child Neurol 2007; 22: 689-692.
[22] Behmanesh F, Ashrafzadeh F, Varasteh A, Shakeri A and Shahsavand S. Evaluation of interleukin 1 [beta] in febrile convulsion. Iran J Allergy Asthma Immunol 2012; 11: 336.
[23] Youn Y, Kim S, Sung I, Chung S, Kim Y and Lee I. Serial examination of serum IL-8, IL-10 and IL-1Ra levels is significant in neonatal seizures induced by hypoxic-ischaemic encephalopathy. Scand J Immunol 2012; 76: 286-293.
[24] Tombini M, Squitti R, Cacciapaglia F, Ventriglia M, Assenza G, Benvenga A, Pellegrino G, Campana C, Assenza F and Siotto M. Inflammation and iron metabolism in adult patients with epilepsy: does a link exist? Epilepsy Res 2013; 107: 244-252.
[25] Uludag IF, Duksal T, Tiftikcioglu BI, Zorlu Y, Ozkaya F and Kirkali G. IL-1β, IL-6 and IL-1Ra levels in temporal lobe epilepsy. Seizure 2015; 26: 22-25.
[26] Ishikawa N, Kobayashi Y, Fujii Y and Kobayashi M. Increased interleukin-6 and high-sensitivity C-reactive protein levels in pediatric epilepsy patients with frequent, refractory generalized motor seizures. Seizure 2015; 25: 136-140.
[27] Choi J and Koh S. Role of brain inflammation in epileptogenesis. Yonsei Med J 2008; 49: 1-18.
[28] Fukuda M, Suzuki Y, Ishizaki Y, Kira R, Kikuchi C, Watanabe S, Hino H, Morimoto T, Hara T and Ishii E. Interleukin-1β enhances susceptibility to hyperthermia-induced seizures in developing rats. Seizure 2009; 18: 211-214.
[29] Haspolat Ş, Baysal Y, Duman Ö, Coşkun M, Tosun Ö and Yein O. Interleukin-1α, interleukin-1β, and interleukin-1Ra polymorphisms in febrile seizures. J Child Neurol 2005; 20: 565-568.
[30] De Sarro G, Russo E, Ferreri G, Giuseppe B, Flocco MA, Di Paola ED and De Sarro A. Seizure susceptibility to various convulsant stimuli of knockout interleukin-6 mice. Pharmacol Biochem Behav 2004; 77: 761-766.
[31] Liimatainen S, Fallah M, Kharazmi E, Peltola M and Peltola J. Interleukin-6 levels are increased in temporal lobe epilepsy but not in extra-temporal lobe epilepsy. J Neurol 2009; 256: 796-802.