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REVIEW

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Blood and CSF biomarkers for post-stroke epilepsy: a systematic review

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Abstract

Post-stroke epilepsy is a common complication of ischemic stroke which adversely affects the prognosis of patients. Clinical and radiological parameters cannot adequately predict the risk. Therefore, the discovery of biomarkers is imperatively needed for predicting post-stroke epilepsy. We conducted a systematic review of diagnostic and prognostic biomarkers for post-stroke epilepsy through a comprehensive literature search in different databases. All articles that met our inclusion criteria were assessed for quality using the modified Quality Assessment of Diagnostic Accuracy Studies questionnaire. Eight eligible studies were included in this systematic review. Out of 22 assessed biomarkers, nine biomarkers showed significant association with post-stroke epilepsy. The T allele of *CD40* (cluster of differentiation 40) −1C/T polymorphism, the CC genotype of *TRPM6* (transient receptor potential cation channel subfamily M member 6) rs2274924, the allele polymorphism of *MAD2* (mitochondrial aldehyde dehydrogenase 2), the mRNA level of interleukin-6 (IL-6), the plasma level of endostatin, and the mRNA expression of IL-1β show a positive correlation with post-stroke epilepsy; while S100 calcium-binding protein B, heat shock 70 kDa protein-8 and neuropeptide Y are inversely associated with post-stroke epilepsy. As a small number of patients were recruited, further studies are needed to confirm their potential use for predicting post-stroke epilepsy.

Keywords: Post-stroke epilepsy, Biomarker, Stroke, Blood and CSF biomarker, Systematic review

Background

Epilepsy is one of the common neurological diseases globally. According to World Health Organisation 2019 updates, around 50 million people are experiencing epilepsy worldwide. Stroke is one of the major causes of epilepsy, accounting for 11% of all epilepsy and 45% of newly diagnosed epilepsy in elderly patients [1]. Post-stroke epilepsy (PSE) has an incidence ranging from 2% to 20% [2].

PSE is induced by various pathogenic factors for epileptogenesis in the brain, leading to recurrent and spontaneous seizures. There is evidence that stroke is one of the primary epileptogenic factors in patients with epilepsy, particularly in the elderly [2]. PSE can sometimes be confused as stroke. This accounts for almost half of the recently analysed epilepsy among patients of over 60 years of age [3].

After a stroke, a cascade of molecules such as damage-associated molecular patterns, cytokines, chemokines, complement factors, prostaglandins, and transforming growth factor beta are released to fix the cerebral outcome. Ongoing neuroinflammation can lead to astroglial and neuronal damage that leads to gliosis and permanent synaptic changes, which in turn lead to abnormal neurogenesis and synaptic transmission. This series of changes may be associated with epileptogenesis [4, 5].

Identification of non-invasive biomarkers of post-stroke epilepsy would be useful for identifying patients at risk and targeting them with proper anti-epileptic drugs, thereby decreasing the morbidity and mortality of the patients. Therefore, we conducted a systematic review on different biomarkers that could predict the risk of future epilepsy in patients with stroke.

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Methods

Inclusion and exclusion criteria

PSE was defined as a single, unprovoked seizure in stroke patients occurring within 1 week of stroke onset. Post-stroke seizure was defined as any seizure occurring after a stroke. There are controversies regarding the definition of the two terms and for the present review, the two terms are used interchangeably [6].

All case-control studies and randomised trials conducted in humans that provide direct link between PSE and biomarkers (including CSF, blood, plasma and serum biomarkers) were included in this systematic review. Pre-clinical studies, model studies, reviews, chapters, newsletters, case reports and studies that did not provide direct link between biomarkers and PSE were excluded.

Literature search

The investigators (PD and AP) performed the literature review and systematic search in 5 electronic databases: PubMed, Science Direct, Embase, Web of Science and Scopus till the date of June 27, 2021. The MeSH terms used for the search were Post-stroke epilepsy [TIAB] OR Post-stroke seizures [TIAB] AND biomarkers [TIAB] (blood, CSF, plasma, serum). The literature search was performed independently and in the case of dispute, consensus was reached after discussion with the third author KC.

Study selection and data extraction

The systematic search was well assisted with the thoroughly defined inclusion and exclusion criteria. After screening the whole study, the relevant information of each article was added in a well-defined table for further analysis and understanding. The table included information like author's name, year of publishing, study population, duration of study, study design, sample size, age and sex, biomarkers evaluated, sample collection, assay method, relevant result, limitation, sensitivity and specificity (Table 1).

Quality assessment

The Modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was used to assess the methodological quality of each study and the quality of diagnostic studies. Two authors PD and AP performed the quality assessment independently. All disagreements regarding quality scores were resolved by discussion and agreement with all authors (Table 2).

Results

We obtained 26 articles from PubMed, of which nine were relevant. Six were original articles and included for the systematic review, while the other three were excluded as they were review articles. The search in the Science Direct database resulted in 43 related articles, of which two were relevant but excluded due to duplication. While the Embase database provided 82 results with seven relevant articles, only one article was included for systematic review. The rest were excluded due to duplication and non-English language. The search in the Web of Science resulted in 60 articles, out of which 6 were relevant but 5 of them were excluded due to duplication and one article was included for the review (Fig. 1). The systematic review has been registered to PROSPERO with registration ID CRD42021271106.

In total, eight articles were eligible and included in the systematic review. The general characteristics of the included studies are described in Table 1. Of them, three were nested case-control and 5 had a case-control design. All the studies were published between 2014 and 2020, and the high quality of the selected records was assured by the QUADAS tool (Table 2).

The study conducted by Zhang et al. investigated the effect of *CD40* polymorphism in PSE. The authors found that the frequency of T allele of CD40-E1SNP (−1C/T) was significantly lower in ischemic stroke (IS) patients when compared to PSE patients (38.5% *vs* 50.5% $P=0.0000017$, OR = 1.628, 95% CI: 1.335–1.986), and the proportion of carriers of this allele was higher in the PSE group than in the IS patients (70.4% *vs* 58.8%, $P=0.00058$, OR = 1.671, 95% CI: 1.246–2.241). The study also revealed a positive association between plasma soluble CD40 ligand level and the risk of PSE [7].

In the study by Abraira et al., 14 blood biomarkers were assessed for their predictive value for PSE, using blood samples collected within 6 h of the stroke. The authors concluded that increased plasma levels of endostatin > 1.203 unit ($P=0.046$, HR 4.300, 95% CI 1.028–17.996), and low levels of heat shock 70 kDa protein-8 (Hsc70) < 2.496 ($P=0.006$, HR 3.795, 95% CI 1.476–9.760) and S100 calcium-binding protein B (S100B) < 1.364 ($P=0.001$, HR 2.955, 95% CI 1.534–5.491) are predictive of PSE. In addition, the risk of PSE increases to 16.8% in the presence of the three factors, compared to 2.6% and 5.0% in the presence of 1 and 2 factors, respectively. The sensitivity of PSE prediction is higher when combining clinical variables with the blood biomarkers (74.3%) than using clinical variables alone (68.9%) [8].

The study conducted by Zhang et al. elaborated that the IL-1β expression level is strongly associated with recurrence after the first epileptic seizure in ischemic stroke

Table 1 Biomarkers for post-stroke epilepsy

Study	Duration of study	Biomarker	Study design	Case-control sample size	Sex and age	Duration of stroke	Assay used	Conclusion	Results	Limitation	Sensitivity	Specificity
Zhang et al. 2014 (China) [7]	September 2010 to April 2013	CD40	Case-control study	410 IS patients, 389 PSE patients, and 160 healthy controls	Males and females	48 h	Immunoassay, Real-time PCR analysis	The frequency of T allele and sCD40L level were significantly higher in PSE patients than in IS patients.	The T allele of the CD40 — 1C/T polymorphism may be associated with PSE susceptibility. The CD40/CD40L system is involved in the process of PSE.	Sample size is relatively small. Cell experiments were not conducted to reveal the pathogenic mechanism	–	–
Abraira et al. 2020 (Spain) [8]	2012–2017	d-dimer, Endostatin, FasL, S100B, Hsc70, APO CIII, GroA, IL-6, NT-proBNP, VAP-1, vWF, IGFBP-3, TNF-R1, NCAM	Nested case-control	45/752 (of 752 IS patients, 45 had PSE, and 707 were non-PSE or taken as control)	Males and females	6 h	Immunoassay	The high level of endostatin > 1.203 and low levels of Hsc70 and S100B < 1.364 had strong positive associations with PSE.	Increased level of endostatin and decreased levels of Hsc70 and S100B may be associated with PSE.	There can be a negative impact on the number of late seizures because of increased number of loss-of-follow up due to death.	–	–
Zhang et al. 2020 (China) [9]	June 2013 to June 2018	IL-1β	Nested case-control	107 IS patients with seizure recurrence, 131 IS patients without seizure recurrence	Males and females 54–73 years	–	Quantitative real-time PCR (qRT-PCR)	IL-1β expression level was higher in patients with seizure recurrence than in patients without recurrence.	IL-1β might be a useful biomarker for early discovery of recurrence after the first epileptic seizure in IS patients.	–	70.09%	87.02%

Table 1 (continued)

Study	Duration of study	Biomarker	Study design	Case-control sample size	Sex and age	Duration of stroke	Assay used	Conclusion	Results	Limitation	Sensitivity	Specificity
Fu et al. 2109 (China) [10]	2014 to 2018	TRPM6 rs2274924, Mg2+.	Case- control	378 PSE patients/420 stroke patients	Males and females	–	PCR analysis, ion selective electrode method	Among 3 genotypes (TT, CT, and CC) of TRPM6, the frequency of the CC genotype was significantly higher in the PSE patients than in the controls	The increased frequency of CC genotype was significantly associated with PSE.	Further studies are needed for the exact understanding of molecular mechanisms.	–	–
Eriksson et al. 2020 (UK) [11]	2013 to 2016	tau, NFL, GFAP, S100b, NSE	Case control	4 PSE patients with thrombectomy /86 IS patients with thrombectomy	Males and females	2 h, 24 h, 48 h, 72 h, and at three months.	Tau or GFAP kit Single molecule array (Simoa) 2.0 assays	Tau protein showed 100% sensitivity and 73% specificity. Other bio-markers (NFL, GFAP, S100B, and NSE) showed 100% sensitivity and 77%–93% specificity	All blood biomarkers displayed interesting sensitivity and specificity.	Small sample size	100%	Tau protien: 73%, NFL, GFAP, S100B, or NSE: 77–93%
Jia et al. 2020 (China) [12]	March 2013 to March 2018	IL-6 mRNA	Nested case control	105 PIS patients with recurrent seizures /104 PIS patients without recurrent seizures	Males and females 37–82 years.	–	qRT-PCR	The expression of IL-6 mRNA was higher in the case group than in the control group.	IL-6 was independently correlated with seizure recurrence in patients with the first post-ischemic stroke seizure	The study had a retrospective design. An unequivocal distribution of the follow-up period,	68.57%	75.00%.

Table 1 (continued)

Study	Duration of study	Biomarker	Study design	Case-control sample size	Sex and age	Duration of stroke	Assay used	Conclusion	Results	Limitation	Sensitivity	Specificity
Yang et al. 2014 (China) [13]	–	ALDH2 rs671	Case- control	225 PSE patients, 240 IS patients and 267 healthy controls	Males and females	–	Polymerase chain reaction-restriction fragment length polymorphism	The frequency of rs671 A allele was higher in the PSE patients compared to the IS patients.	There is a positive association between ALDH2 polymorphism and PSE.	The study did not provide exact role of ALDH2 in PSE	–	–
Wang et al. 2021 (China) [14]	January 2015 to December 2018	Neuropeptide Y	Case- control	78 PISE patients /86 IS patients	Males and females	24 h	ELISA detection	Neuropeptide Y was inversely associated with PSE.	There was a 62% risk reduction in PISE patients with every 5 ng/ml increment of serum NPY.	Short duration of study, and sample size of the study was small	84.62%	86.05%

* *ApoCIII* apolipoprotein CIII, *FasL* Fas ligand, *GroA* growth-related oncogene α, *Hsc70* Heat shock 70 kDa protein-8, *IGFBP-3* insulin-like growth factor binding protein-3, *IL-6* interleukin 6, *NCAM* neural cell adhesion molecule, *NT-proBNP* N-terminal Pro-B-type natriuretic peptide, *S100B* S100 calcium-binding protein B, *TNF-R1* tumor necrosis factor, *VAP-1* vascular adhesion protein-1, *vWF* von Willebrand factor, *IL-1β* Inter leucine- one beta, *TRPM6* transient receptor potential cation channel subfamily M member 6, *NFL* neurofilament light, *GFAP* glial fibrillary acidic protein, *S100B* S100 calcium-binding protein B, *NSE* neuron-specific enolase, *ALDH2* Mitochondrial aldehyde dehydrogenase 2, *NPY* Neuropeptide Y

Table 2 Quality assessment of each study included in this systematic review by using the modified QUADAS questionnaire

Study	All patients had same reference standard test	All patients had reference standard whether BM+/BM-	Biomarker status not part of epilepsy diagnosis	Biomarker measurement blind to stroke status	Clinical/Radiology opinion blind to biomarker status	All the patients who entered the study had results reported	Diagnostic threshold established before study
Zhang et al. 2014 (China) [7]	1	1	1	0	1	1	0
Abraira et al. 2020 (Spain) [8]	1	1	1	0	1	1	0
Zhang et al. 2020 (China) [9]	1	1	1	0	1	1	0
Fu et al. 2109 (China) [10]	1	1	1	0	1	1	0
Eriksson et al. 2019 (U.K [11]	1	1	1	0	1	1	0
Jia et al. 2020 (China) [12]	1	1	1	0	1	1	0
Yang et al. 2014 (China) [13]	1	1	1	0	1	1	0
Wang et al. 2021 (China) [14]	1	1	1	0	1	1	0

and can be used to estimate the risk of recurrent epileptic seizures. The authors found that the IL-1β mRNA expression level was higher in patients with seizure recurrence (6.49 vs 3.18, $n=238$, $P<0.05$). The sensitivity and specificity of IL-1β expression in predicting PSE were 70.09% and 87.02%, respectively [9].

Fu et al. studied the role of functional polymorphism of transient receptor potential cation channel subfamily M member 6 (*TRPM6*) rs2274924 in the susceptibility to epilepsy following ischemic stroke. Sequencing of *TRPM6* found 3 rs2274924 genotypes (TT, CT, and CC), and the frequency of the CC genotype was significantly higher in the PSE patients than in the controls ($P=0.006$). The authors also provided evidence of increased expression of the rs2274924 C allele in the PSE patients in comparison to the controls (37.1% *vs* 30.2%, $\chi^2=8.578$, $P=0.003$), which was strongly associated with the low serum concentration of Mg^{2+} [10].

The study conducted by Eriksson et al. investigated the incidence of PSE in patients treated with mechanical thrombectomy. While analyzing the relationship between blood biomarkers and PSE, they found that the tau protein had 100% sensitivity and 73% specificity. Other biomarkers (Neurofilament light, glial fibrillary acidic protein, S100B, or neuron-specific enolase showed 100% sensitivity with 77%–93% specificity. However, they also mentioned the need for further studies due to the low incidence of PSE in their cohort [11].

Jia et al. conducted a study to evaluate the relationship between IL-6 and seizure recurrence in patients with the first post-ischemic stroke seizure. They found higher expression of IL-6 mRNA in the case group than in the control group (6.32 ± 2.18 *vs* 3.41 ± 1.64, $t=10.912$, $P<0.001$), and concluded that IL-6 can be used as a predictor for recurrence of seizure [12].

In a case-control study, Yang et al. reported that the SNP rs671 of aldehyde dehydrogenase 2 (ALDH2) is related with susceptibility to PSE. They also found that the 4-hydroxynonenal (4-HNE) level was increased in stroke patients and PSE patients, compared to the control. Because of the connections between ALDH2 and 4-HNE, they next assessed the impact of the rs671 polymorphism of ALDH2 on 4-HNE levels, and as expected, they found increased 4-HNE levels in carriers of the ALDH2*2 allele. In PC12 cells, overexpression of ALDH2 diminished the degree of oxidative pressure and apoptosis induced by 4-HNE. They found that the frequency of the rs671 A allele was higher in the PSE patients than in

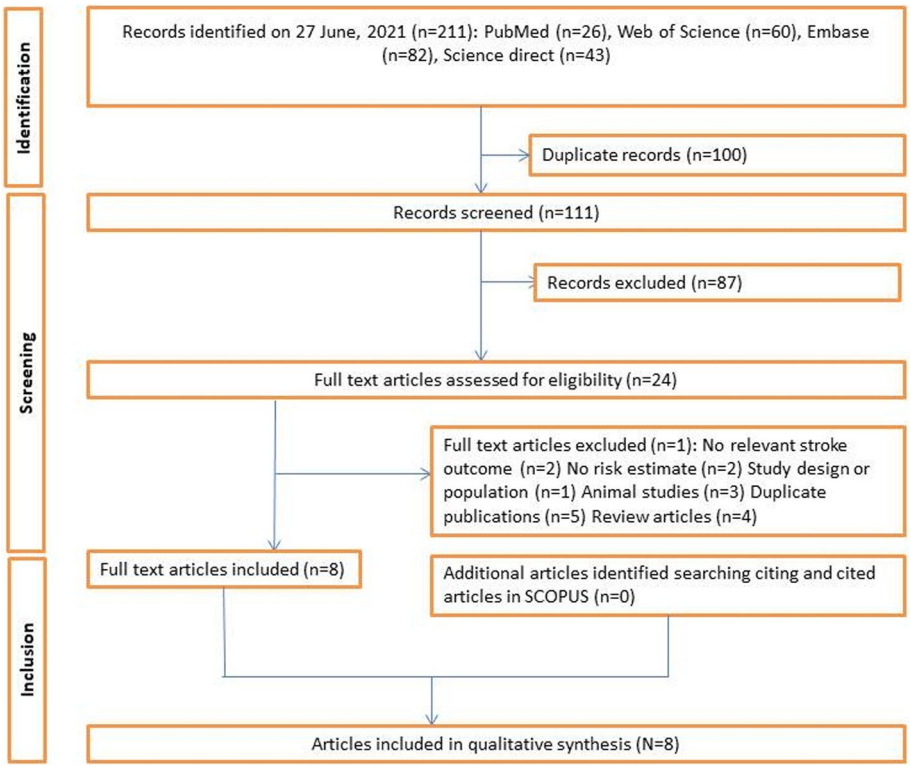

Fig. 1 Study flow chart

the IS patients (31.8% *vs* 21.3%, $P=0.00036$, OR = 1.98, 95%CI = 1.36–2.87) [13].

The study conducted by Wang et al. analyzed the role of neuropeptide Y (NPY) in PSE. They found that NPY was inversely associated with PSE, as the concentration of NPY was significantly lower in PSE cases (85 ng/ml) than in the controls (107.50 ng/ml) ($P<0.001$). The risk was reduced by 62% in post-ischemic stroke epilepsy (PISE) patients with every 5 ng/ml increment of serum NPY [14]. Of these studies, only Erikson et al. and Wang et al. reported sensitivity and specificity of biomarkers assessed; other authors did not report the sensitivity and specificity of the studied biomarkers. We tried to contact the corresponding authors by email, but no reply was received.

Discussion

As far as we know, this is the first systematic review on biomarkers of PSE. Out of 22 assessed biomarkers, 9 biomarkers showed significant associations with PSE. The T allele of the CD40 − 1C/T polymorphism, the CC genotype of TRPM6 rs2274924, the ALDH2 rs671 polymorphism, the levels of IL-6 and IL-1β mRNA expression, and the plasma level of endostatin, show positive correlations with PSE, while S100B, Hsp70 and NPY are inversely associated with PSE. The study by Erikson et al. in patients with post-thrombectomy stroke showed that Tau protein has a sensitivity of 100% and a specificity of 73%, while NFL, GFAP, S100B, or NSE also had a sensitivity of 100% and a specificity of 77%–93% for PSE. Another study by Wang et al. showed that NPY had a sensitivity and a specificity of 84.6% and 86.5%, respectively, in predicting PSE.

Inflammation plays a central role in brain injury caused by stroke, and post-stroke inflammation is mainly guided by microglia and astrocytes in the brain tissue [15–18]. Interleukins such as IL-1β and IL-6 have been found to be associated with the initiation and progression of different types of epilepsy [19]. CD40 and CD40 ligand (CD40L) belong to the tumor necrosis factor superfamily and the tumor rot factor family, respectively [20, 21]. After activation of platelet and cytokines, the CD40/CD40L framework is initiated, which ultimately up-regulates the coagulant qualities in patients [22]. In any case, there are few data on the impact of CD40-associated polymorphisms on PSE. However, there is evidence that the CD40 − 1C/T polymorphism is related to PSE, and people with a T allele have a higher rate of epilepsy post stroke [7]. Loss of NPY and overexpression of NPY in the hippocampus

in animal models have been found to be associated with severe epileptic seizures and inhibition of epileptic activity, respectively [23–25].

Recent research on PISE showed that in the context of ischemic injury, the microscale changes in veins and white matter which are hard to identify may contribute to the epileptogenic pathology [26]. This suggests that the epileptogenic components are less well understood, which makes it hard to estimate the likelihood of PISE. Despite the fact that in some patients, hazard factors that add to epileptogenesis after stroke are hard to determine [27], previous investigations have revealed some factors related to PSE, including stroke subtype, cortical inclusion, enormous localized necrosis, and stroke severity [28].

Our systemic review has major limitations. First, except from one study by Zhang et al., the studies included in this review had small sample size and various timings of patient recruitment, which could affect the overall validity of the results. Second, the different studies tested different biomarkers, which has limited the external validity of each of the molecules. Third, only three of the eight studies have reported the sensitivity and specificity of biomarkers assessed. We attempted to contact the corresponding authors by email for these data, but no reply was received. Fourth, the studies have used ELISA-based assays to study the biomarkers, but MALDI-TOF remains the most sensitive and standard method of estimation. Fifth, as mentioned earlier, the studies have analyzed different biomarkers in the discovery phase, but failed to validate them in larger populations in a phase-wise manner from phase 0 which is the pre-clinical phase to phase 4 which is a large surveillance cohort study. The effectiveness of any new diagnostic strategy in clinical practice needs evaluation in all of the stages. Sixth, only the study by Eriksson et al. had a longitudinal prospective design. The other studies were performed retrospectively. None of the published studies used any blinding and concealment methods to mask the group information and the levels of the corresponding biomarkers.

Future directions

For resource-poor countries, blood biomarkers can facilitate the diagnosis of PSE, which would lead to better management of patients, prevent hospitalisation, and decrease morbidity and mortality of patients. Future studies on the potential of different biomarkers to predict PSE should employ larger population sizes and cover different phases from diagnostics to validation. The control population should include both age-matched healthy population and post-stroke patients who did not develop epilepsy. Newer methods such as MALDI-TOF, metabolomics, and whole-genome sequencing should be explored for the discovery of new biomarkers.

Conclusions

The present systematic review suggests that increased frequency of T allele of the CD40–1C/T and CC genotype of TRPM6 rs2274924 are associated with PSE. The low levels of S100B and Hsc70, and high levels of endostatin attenuate the risk of PSE in IS patients. Two studies suggested the overexpression of IL-1β and IL-6 as indicators for PSE, and one study showed that Tau protein and other blood biomarkers NFL, GFAP, S100B and NSE had 100% sensitivity for PSE. The study of ALDH2 polymorphism in PSE patients also showed a positive association. NPY is inversely associated with PSE. However, due to several limitations, no single biomarkers can be suggested for clinical use at this point of time. Further prospective studies in large populations using better techniques are needed to establish biomarkers for prediction of PSE.

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Authors' contributions
Priya Dev- Study design, database search, data extraction and manuscript writing. Mareena Cyriac- Data extraction and manuscript writing. Kamalesh Chakravarty- Study design and Data extraction. Abhishek Pathak- Study design, database search, data extraction and manuscript editing. The authors read and approved the final manuscript.

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References

1. Xu MY. Poststroke seizure: optimising its management. Stroke Vasc Neurol. 2019;4(1):e000175. https://doi.org/10.1136/svn2018-000175.

2. Feyissa AM, Hasan TF, Meschia JF. Stroke-related epilepsy. Eur J Neurol. 2019;26(1):18–e3.
3. Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia. 1996;37(3):224–9.
4. Henshall D, Engel T. Contribution of apoptosis-associated signaling pathways to epileptogenesis: lessons from Bcl-2 family knockouts. Front Cell Neurosci. 2013;16(7):110.
5. Vezzani A, Balosso S, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nat Rev Neurol. 2019 Aug;15(8):459–72.
6. Tanaka T, Ihara M. Post stroke epilepsy. Neurochem Int. 2017;107:219–28.
7. Zhang B, Chen M, Yang H, Wu T, Song C, Guo R. Evidence for involvement of the CD40/CD40L system in post-stroke epilepsy. Neurosci Lett. 2014;1(567):6–10.
8. Abraira L, Santamarina E, Cazorla S, Bustamante A, Quintana M, Toledo M, et al. Blood biomarkers predictive of epilepsy after an acute stroke event. Epilepsia. 2020;61(10):2244–53.
9. Zhang Q, Li G, Zhao D, Yang P, Shabier T, Tuerxun T. Association between IL-1β and recurrence after the first epileptic seizure in ischemic stroke patients. Sci Rep. 2020;10(1):1–8.
10. Fu CY, Chen SJ, Cai NH, Liu ZH, Zhang M, Wang PC, et al. Increased risk of post-stroke epilepsy in Chinese patients with a TRPM6 polymorphism. Neurol Res. 2019;41(4):378–83.
11. Eriksson H, Hendén PL, Rentzos A, Pujol-Calderón F, Karlsson JE, Höglund K, et al. Acute symptomatic seizures and epilepsy after mechanical thrombectomy. Epilepsy Behav. 2020;104:106520.
12. Jia Q, Jiang F, Ma D, Li J, Wang F, Wang Z. Association between IL-6 and seizure recurrence in patients with the first post-ischemic stroke seizure. Neuropsychiatr Dis Treat. 2020;16:1955.
13. Yang H, Song Z, Yang GP, Zhang BK, Chen M, Wu T, et al. The ALDH2 rs671 polymorphism affects post-stroke epilepsy susceptibility and plasma 4-HNE levels. PLoS One. 2014;9(10):e109634.
14. Wang N, Wang D, Zhou H, Xu C, Hu X, Qian Z, et al. Serum neuropeptide Y level is associated with post-ischemic stroke epilepsy. J Stroke Cerebrovasc Dis. 2021;30(2):105475.
15. Di Napoli M, Papa F, Bocola V. C-reactive protein in ischemic stroke: an independent prognostic factor. Stroke. 2001;32(4):917–24.
16. Whiteley W, Jackson C, Lewis S, Lowe G, Rumley A, Sandercock P, et al. Inflammatory markers and poor outcome after stroke: a prospective cohort study and systematic review of interleukin-6. PLoS Med. 2009;6(9):e1000145.
17. Benakis C, Garcia-Bonilla L, Iadecola C, Anrather J. The role of microglia and myeloid immune cells in acute cerebral ischemia. Front Cell Neurosci. 2015;8:461.
18. Roy-O'Reilly M, McCullough LD. Astrocytes fuel the fire of lymphocyte toxicity after stroke. Proc Natl Acad Sci. 2017;114(3):425–7.
19. Shi LM, Chen RJ, Zhang H, Jiang CM, Gong J. Cerebrospinal fluid neuron specific enolase, interleukin-1β and erythropoietin concentrations in children after seizures. Child's Nerv Syst. 2017;33(5):805–11.
20. Anand SX, Viles-Gonzalez JF, Badimon JJ, Cavusoglu E, Marmur JD. Membrane-associated CD40L and sCD40L in atherothrombotic disease. Thromb Haemost. 2003;90(09):377–84.
21. Prasad ML, Velickovic M, Weston SA, Benson EM. Mutational screening of the CD40 ligand (CD40L) gene in patients with X linked hyper-IgM syndrome (XHIM) and determination of carrier status in female relatives. J Clin Pathol. 2005;58(1):90–2.
22. Antoniades C, Bakogiannis C, Tousoulis D, Antonopoulos AS, Stefanadis C. The CD40/CD40 ligand system: linking inflammation with atherothrombosis. J Am Coll Cardiol. 2009;54(8):669–77.
23. Sun Z, Liu S, Kharlamov EA, Miller ER, Kelly KM. Hippocampal neuropeptide Y protein expression following controlled cortical impact and posttraumatic epilepsy. Epilepsy Behav. 2018;87:188–94.
24. Ledri LN, Melin E, Christiansen SH, Gøtzsche CR, Cifra A, Woldbye DP, et al. Translational approach for gene therapy in epilepsy: model system and unilateral overexpression of neuropeptide Y and Y2 receptors. Neurobiol Dis. 2016;86:52–61.
25. Richichi C, Lin EJ, Stefanin D, Colella D, Ravizza T, Grignaschi G, et al. Anticonvulsant and antiepileptogenic effects mediated by adeno-associated virus vector neuropeptide Y expression in the rat hippocampus. J Neurosci. 2004;24(12):3051–9.
26. Pitkänen A, Roivainen R, Lukasiuk K. Development of epilepsy after ischaemic stroke. Lancet Neurol. 2016;15(2):185–97.
27. Zhao Y, Li X, Zhang K, Tong T, Cui R. The progress of epilepsy after stroke. Curr Neuropharmacol. 2018;16(1):71–8.
28. Zhang C, Wang X, Wang Y, Zhang JG, Hu W, Ge M, et al. Risk factors for post-stroke seizures: a systematic review and meta-analysis. Epilepsy Res. 2014;108(10):1806–16.