Polymorphism of *IL-1B* rs16944 (T/C) associated with serum levels of IL-1β affects seizure susceptibility in ischemic stroke patients

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Abstract

Background. Seizures and the subsequent development of epilepsy after stroke may not only hinder patient's recovery but also increase the risk of complications. Interleukin (IL)-1β has been shown to be acutely upregulated after ischemic stroke and play a role in the recurrence of seizures following the first epileptic seizure in patients suffering an ischemic stroke. Meanwhile, variants of the *IL-1B* gene encoding IL-1β are involved in the stimulation of febrile seizures.

Objectives. To study the potential associations of the 5 polymorphisms of the *IL-1B* gene with seizure susceptibility in ischemic stroke patients, and to explore the possible mechanisms.

Materials and methods. A total of 856 ischemic stroke patients were allocated into the control group (patients without post-stroke seizures) and the case group (patients with post-stroke seizures). The *IL-1B* polymorphisms rs10490571 (T/C), rs114363 (C/T), rs1143623 (G/C), rs16944 (T/C), and rs2853550 (A/G) were detected using TaqMan SNP genotyping assays, and serum IL-1β levels were measured using the enzyme-linked immunosorbent assay (ELISA). Demographic data, clinical characteristics and cerebrovascular disease risk factors at admission were collected. Multivariate analysis was performed to determine independent associations, and IL-1β levels were compared using analysis of variance (ANOVA) followed by a post hoc test.

Results. In 74 patients (8.6%, 74/856), post-stroke seizures occurred within 1 year of stroke onset. The multivariate analysis showed that the rs16944 polymorphism of *IL-1B*, cortical involvement and National Institutes of Health Stroke Scale (NIHSS) score on admission were correlated with post-stroke seizures after adjusting for stroke laterality, thrombolysis, use of statins, and IL-1B rs10490571. The IL-1B rs16944 TT (odds ratio (OR): 1.923, 95% confidence interval (95% CI): 1.257–4.185) and TC genotypes (OR: 1.469, 95% CI: 1.130–2.974) were associated with a significantly increased risk of post-stroke seizures compared to the CC genotype. One-way ANOVA for IL-1β levels demonstrated a tendency for higher levels in TT > TC > CC genotypes (6.41 compared to 4.53 compared to 2.10 pg/mL, respectively).

Conclusions. The *IL-1B* rs16944 polymorphism had an independent association with seizure susceptibility after ischemic stroke. The mechanism might be associated with the regulation of IL-1β levels.

Key words: polymorphism, multivariate analysis, *IL-1B* rs16944 (T/C), post-stroke seizures, IL-1β levels

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Background

Strokes are the 2nd leading cause of preventable deaths around the world and the primary cause of long-term disability.[1] In China, the stroke burden has been increasing over the past 30 years. The age-standardized incidence has risen to 246.8/100,000 person-years, and the age-standardized mortality to 114.8/100,000 person-years.[2] Ischemic stroke, which accounts for 75–80% of all strokes, is the most common cause of seizures among the elderly and is the predominant cause of seizures among the adults.[3–5] Seizures and the subsequent development of epilepsy after stroke may not only hinder patient's recovery but also increase the risk of complications.[6] With demographic changes, the healthcare system is facing a challenge of an increasing number of elderly people with post-stroke seizures. Therefore, the identification and appropriate management of stroke patients with an increased susceptibility for seizures are crucial in stroke care. Interleukin (IL)-1β has been demonstrated to be acutely upregulated after an ischemic stroke and be involved in the recurrence of seizures following the first epileptic seizure in patients with ischemic strokes.[7–9] At the same time, variants of the *IL-1B* gene encoding IL-1β have been shown to be involved in the stimulation of febrile seizures.[10] Additionally, the *IL-1B* polymorphisms rs16944, rs1143623, rs10490571, and rs2853550 were associated with the expression of IL-1β. However, the correlations between these polymorphisms and post-stroke seizures have not been analyzed.

Objectives

In this study, the association of *IL-1B* polymorphisms rs10490571, rs114363, rs16944, rs1143623, and rs2853550 with post-stroke seizures was determined using multivariate analysis. This study aimed to evaluate the potential associations of 5 polymorphisms of the *IL-1B* gene with seizure susceptibility in ischemic stroke patients, and to explore the possible mechanisms.

Materials and methods

Participants

This case-control study was performed at the Shandong Provincial Third Hospital (Jinan, China) between September 2018 and August 2019, and included 856 ischemic stroke patients into the final analysis. Participants meeting the following criteria were included: 1) acute first-ever ischemic stroke definitively diagnosed using magnetic resonance imaging (MRI) or computed tomography (CT); 2) ≥18 years of age at the time of admission; 3) no previous history of seizures; 4) no potentially epileptogenic comorbidities such as cerebral venous thrombosis, cerebral arteriovenous malformations, intracranial tumors, etc.; 5) complete medical data; and 6) the ability to provide written informed consent. Participants with the following characteristics were excluded: 1) history of antiepileptic drug therapy to prevent seizures or other diseases; 2) primary hemorrhagic stroke or transient ischemic attacks; and 3) lost to follow-up or death before the follow-up. This study received the approval from the Ethical Committee of Shandong Provincial Third Hospital (approval No. SDTH-201813022).

Grouping

All 856 ischemic stroke patients were allocated either into the control group (patients without post-stroke seizures) or the case group (patients with post-stroke seizures), depending on the occurrence of a post-stroke seizure within 1 year of the onset of ischemic stroke. The diagnosis of seizure occurrence was determined using the definition provided by the International League Against Epilepsy (ILAE).

Data collection

We retrospectively collected the demographic data, clinical characteristics and cerebrovascular disease risk factors of participants at admission. The demographic data included sex, age and body mass index (BMI), while cerebrovascular disease risk factors included hypertension, smoking, drinking, diabetes mellitus, coronary heart disease, dyslipidemia, and atrial fibrillation. The clinical characteristics including stroke laterality, cortical involvement, the National Institutes of Health Stroke Scale (NIHSS) score at admission, Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (large artery atherosclerosis, cardioembolism, small vessel occlusion, other determined, and undetermined), stroke treatment methods, and duration from stroke onset to admission were collected.

Genotyping and measurement of IL-1β levels

Peripheral blood samples were collected from all participants and DNA was extracted from the blood samples using the phenol-chloroform method. The concentration of DNA was measured using the optical density, and the quality of DNA was assessed according to the 260/280 ratio. TaqMan™ Pre-Designed SNP genotyping assays (Applied Biosystems, Waltham, USA) were used to detect the polymorphisms (C___29921173_20 for rs10490571, C___9546529_30 for rs114363, C___1839943_10 for rs16944, C___1839941_10 for rs1143623, and C___188872117_10 for rs2853550). Haploview software v. 4.2 (Broad Institute, Cambridge, USA) was used to analyze the Hardy–Weinberg equilibrium (HWE), as well as allele and genotype frequencies.

After the blood samples were centrifuged for 10 min at 3000 g, serum IL-1β levels were measured using the Human Interleukin-1β ELISA Kit (Baiaolaibo, Beijing, China).

Statistical analyses

The IBM SPSS v. 22.0 (IBM Corp., Armonk, USA) was used to perform all statistical analyses, and significance was set at a two-sided p-value <0.05. The Shapiro–Wilk test was used to evaluate the normality of continuous data. The Student's t-test was used to compare the means of normally distributed data between the case group and the control group. The Mann–Whitney U test was used to compare the pseudo-medians of non-normally distributed data. The χ^2 test was used to compare the differences in qualitative data between the case and control groups, and the Fisher's exact test was used when 1 or more cells had an expected count of less than 5. To avoid the omission of variables that might be meaningful and to determine independent associations, the multivariate analysis was performed for variables with a two-sided p-value <0.10 in the univariate analysis, using a backward stepwise logistic regression model. The IL-1β levels were compared using analysis of variance (ANOVA) followed by post hoc testing in ischemic stroke patients with different genotypes.

Results

General results

A total of 74 participants (8.6%, 74/856) had post-stroke seizures within 1 year of stroke onset. In the continuous data, NIHSS score at admission was non-normally distributed and was expressed using the median and the 1st and 3rd quartile (Q1, Q3). The NIHSS score at admission was 14 (12, 18) in the case group and 12 (10, 16) in the control group, and its pseudo-median was compared using the Mann–Whitney U test. Other continuous data were normally distributed, and their means were compared using Student's t-tests. According to the results of univariate analysis, stroke laterality, cortical involvement, thrombolysis, use of statins (Table 1), and NIHSS score on admission ($Z = 2.013$, $p = 0.044$) were significantly different between the control and case groups. Other variables were not significantly different.

Genotyping results

In 841 participants, these 5 single nucleotide polymorphisms (SNPs) were successfully genotyped. Sequencing was further carried out for the SNPs that were not genotyped successfully. Finally, all 856 participants were successfully genotyped for these 5 SNPs. As shown in Table 2, the genotype frequencies of these 5 SNPs were not significantly different from those predicted using the HWE. The χ^2 test showed that the genotype frequencies of *IL-1B* rs16944 (degrees of freedom (df) = 2, $\chi^2 = 8.683$, $p = 0.013$) and rs10490571 (df = 2, Fisher's exact test, $p = 0.030$) were significantly different between the case and control groups, but rs1143623 (df = 2, $\chi^2 = 0.261$, $p = 0.878$), rs114363 (df = 2, Fisher's exact test, $p = 0.456$) and rs2853550 (df = 2, Fisher's exact test, $p = 0.698$) were not.

Multivariate analysis

The multivariate analysis was conducted for the following variables: cortical involvement, stroke laterality, NIHSS score on admission, thrombolysis, use of statins, *IL-1B* rs16944, and *IL-1B* rs10490571. As demonstrated in Table 3, the *IL-1B* polymorphism rs16944, cortical involvement and NIHSS score on admission were correlated with post-stroke seizures after adjusting for stroke laterality, thrombolysis, use of statins, and *IL-1B* rs10490571. The *IL-1B* rs16944 TT and TC genotypes were associated with a significantly increased risk of post-stroke seizures compared to the CC genotype. Moreover, the odds ratio (OR) of the TT genotype was higher than that of the TC genotype.

IL-1β levels

The IL-1β levels in the case group were higher than that of the control group (Student's t-test, $df = 854$, $t = 2.683$, $p = 0.008$, Fig. 1A). One-way ANOVA for IL-1β levels demonstrated a tendency for higher levels in TT compared to TC and CC genotypes (Fig. 1B, 6.41 compared to 4.53 compared to 2.10 pg/mL, respectively; overall test: $F = 10.537$, $p = 0.007$, post hoc results are presented in Table 4).

Discussion

The incidence of post-stroke seizures ranged from 2% to 20% with great variation.[11–13] Post-stroke seizures can lead to additional complications, increased mortality and longer initial hospitalizations, which substantially impact the prognosis and quality of life in stroke patients.[14,15]

Inflammation is extensively involved in the pathophysiology of an ischemic stroke.[16] The expression of pro-inflammatory cytokines, including IL-1β and IL-6, have been found to be significantly upregulated after an acute stroke.[17] Neuroinflammation can result in hyperexcitability, a ground base for seizures.[18,19] In the central nervous system, *IL-1B* is a constitutively expressed gene that can modulate both the expression and activity of ion channels and exert a neurotrophic factor-like activity.[20,21] The levels of inflammatory cytokines in the IL-1β pathway can act as biomarkers for neurologic diseases. The IL-1β can increase neuronal excitability through the activation of its endogenous receptor.[22,23] Following an initial insult to the central nervous system, ongoing inflammation can

Table 1. Univariate analysis results of the differences regarding demographic data, risk factors for cerebrovascular diseases and clinical characteristics between the case group and control group

Variables	All ischemic stroke patients (n = 856)	Case group (n = 74)	Control group (n = 782)	df	Student's t test/χ^2 test	p-value
Demographic data						
Age [years], M ±SD	67.26 ±9.25	68.37 ±9.14	67.15 ±9.26	854	1.096	0.285
Males, n (%)	510 (59.6)	48 (64.9)	462 (59.1)	1	0.940	0.332
BMI [kg/m^2], M ±SD	24.67 ±3.18	25.09 ±3.07	24.63 ±3.19	854	1.228	0.225
Risk factors for cerebrovascular diseases						
Smoking, n (%)	201 (23.5)	21 (28.4)	180 (23.0)	1	1.081	0.298
Alcohol consumption, n (%)	326 (38.1)	25 (33.8)	301 (38.5)	1	0.635	0.425
Diabetes mellitus, n (%)	162 (18.9)	18 (24.3)	144 (18.4)	1	1.539	0.215
Hypertension, n (%)	556 (65.0)	44 (59.5)	512 (65.5)	1	1.074	0.300
Coronary heart disease, n (%)	40 (4.7)	6 (8.1)	34 (4.3)	1	–	0.147*
Dyslipidemia, n (%)	171 (20.0)	19 (25.7)	152 (19.4)	1	1.646	0.200
Atrial fibrillation, n (%)	61 (7.1)	8 (10.8)	53 (6.8)	1	1.474	0.225
Clinical characteristics						
Stroke laterality, n (%)						
Right	418 (48.8)	47 (63.5)	371 (47.4)	1	6.988	0.008
Left	438 (51.2)	27 (36.5)	411 (52.6)			
Cortical involvement, n (%)	199 (23.2)	27 (36.5)	172 (22.0)	1	7.957	0.005
TOAST classification, n (%)						
Large artery atherosclerosis	457 (53.4)	35 (47.3)	422 (54.0)	1	1.207	0.272
Cardioembolism	176 (20.6)	17 (23.0)	159 (20.3)	1	0.289	0.591
Small vessel occlusion	129 (15.1)	8 (10.8)	121 (15.5)	1	1.148	0.284
Other determined	47 (5.5)	2 (2.7)	45 (5.8)	1	–	0.421*
Undetermined	121 (14.1)	12 (16.2)	109 (13.9)	1	0.286	0.592
Stroke treatment, n (%)						
Thrombolysis	79 (9.2)	15 (20.3)	64 (8.2)	1	11.788	0.001
Antiplatelet therapy	600 (70.1)	48 (64.9)	552 (70.6)	1	1.056	0.304
Anticoagulation therapy	255 (29.8)	27 (36.5)	228 (29.2)	1	1.737	0.188
Use of statins	708 (82.7)	55 (74.3)	653 (83.5)	1	3.983	0.046
Duration from stroke onset to admission [h], M ±SD	18.98 ±7.95	19.49 ±7.64	18.93 ±7.98	854	0.600	0.556

M ±SD – mean ± standard deviation; df – degrees of freedom; BMI – body mass index; TOAST – Trial of ORG 101072 in Acute Stroke Treatment; * Fisher's exact test.

change neuronal plasticity through several transcriptionally mediated effects, which have the potential for aberrant and epileptogenic circuits.[24–26] Vezzani et al. reported that IL-1β had proconvulsive effects on limbic seizures in mice induced by electrical stimulation, bicuculine and kainic acid.[27] Šutulović et al. showed that chronic pelvic pain syndrome/chronic prostatitis (CPPS/CP) induced with experimental λ-carrageenan can lead to an increased susceptibility of rats to lindane-induced seizures through the upregulation of IL-6 and IL-1β levels in the thalamus and cerebral cortex.[28]

The mechanisms associated with the proconvulsive effects of IL-1β remain unexplained. Several potential mechanisms refer to IL-1β reducing the seizure threshold through the induction of an intracellular $Ca2^+$ ion surge and resultant modifications on voltage-dependent ion channels[29]; IL-1β stimulating the production of NO in the brain[30]; IL-1β inducing neuronal hyperexcitability through the activation of the N-methyl-D-aspartate receptor (NMDA-R) and stimulating the chronic release of excitatory neurotransmitters[31]; and IL-1β inhibiting K^+ efflux, the recycling of gamma-aminobutyric acid (GABA) receptors, and the uptake of excitatory neurotransmitters by the glial population.[30,32] According to our results, the levels of IL-1β in ischemic stroke patients with post-stroke seizures were significantly higher than in those without post-stroke seizures.

The expression of cytokines can be regulated by polymorphisms within the promoter regions of their genes. Therefore, these promoter polymorphisms can influence the disease susceptibility by mediating the extent of the secretory response of these cytokines.[33,34] The IL-1

Table 2. Results of Hardy–Weinberg equilibrium (HWE) testing in the case and control group

IL-1B polymorphisms		Allele frequency, n		Genotype frequency, n (%)			HWE testing		
							df	χ^2	p-value
rs16944	–	T	C	TT	TC	CC	–		
	case group (n = 74)	83	65	23 (31.1)	37 (50.0)	14 (18.9)	2	1.216	0.253
	control group (n = 782)	675	889	165 (21.1)	345 (44.1)	272 (34.8)	2	0.937	0.328
rs1143623	–	G	C	GG	GC	CC	–		
	case group (n = 74)	60	88	12 (16.2)	36 (48.6)	26 (35.1)	2	2.286	0.131
	control group (n = 782)	601	963	113 (14.4)	375 (48.0)	294 (37.6)	2	1.023	0.305
rs114363	–	C	T	CC	CT	TT	–		
	case group (n = 74)	142	6	68 (91.9)	6 (8.1)	0 (0)	2	–	0.547*
	control group (n = 782)	1516	48	734 (93.9)	48 (6.1)	0 (0)	2	–	0.498*
rs10490571	–	T	C	TT	TC	CC	–		
	case group (n = 74)	35	113	5 (6.8)	25 (33.8)	44 (59.5)	2	1.956	0.170
	control group (n = 782)	241	1323	23 (2.9)	195 (24.9)	564 (72.1)	2	1.542	0.203
rs2853550	–	A	G	AA	AG	GG	–		
	case group (n = 74)	16	132	2 (2.7)	12 (16.2)	60 (81.1)	2	–	0.618*
	control group (n = 782)	151	1413	24 (3.1)	103 (13.2)	655 (83.8)	2	0.172	0.674

df – degrees of freedom; * Fisher's exact test.

Table 3. Results of the multivariate analysis of the differences between the case and control group

Variables	Regression coefficient	Standard error	Wald	OR	95% CI	p-value
rs16944	–	–	7.265	–	–	0.029
CC	–	–	–	–	–	Ref = 1
TC	0.512	0.203	6.017	1.469	1.130–2.974	0.038
TT	0.654	0.231	8.786	1.923	1.257–4.185	0.012
rs10490571	–	–	2.685	–	–	0.153
CC	–	–	–	–	–	Ref = 1
TC	0.376	0.128	2.154	1.293	0.714–2.039	0.186
TT	0.395	0.141	2.978	1.327	0.748–2.191	0.132
Cortical involvement	0.428	0.159	5.982	1.354	1.105–2.893	0.041
Stroke laterality	0.297	0.106	1.839	1.277	0.693–2.012	0.214
NIHSS at admission	0.293	0.102	6.326	1.192	1.058–1.705	0.034
Thrombolysis	0.314	0.125	1.548	1.214	0.549–1.692	0.263
Use of statins	0.258	0.116	1.095	1.189	0.457–1.658	0.327

OR – odds ratio; 95% CI – 95% confidence interval; NIHSS – National Institutes of Health Stroke Scale.

Table 4. Post hoc results of the analysis of the interleukin (IL)-1β levels [pg/mL]

(I) Genotypes	(J) Genotypes	Mean difference (I–J)	Standard error	p-value	95% CI	
					lower bound	upper bound
TT	TC	2.03	0.57	0.011	0.91	3.15
	CC	4.32	0.78	0.002	2.79	5.85
TC	TT	–2.03	0.57	0.011	–3.15	–0.91
	CC	2.29	0.64	0.005	1.04	3.54
CC	TT	–4.32	0.78	0.002	–5.85	–2.79
	TC	–2.29	0.64	0.005	–3.54	–1.04

95% CI – 95% confidence interval.

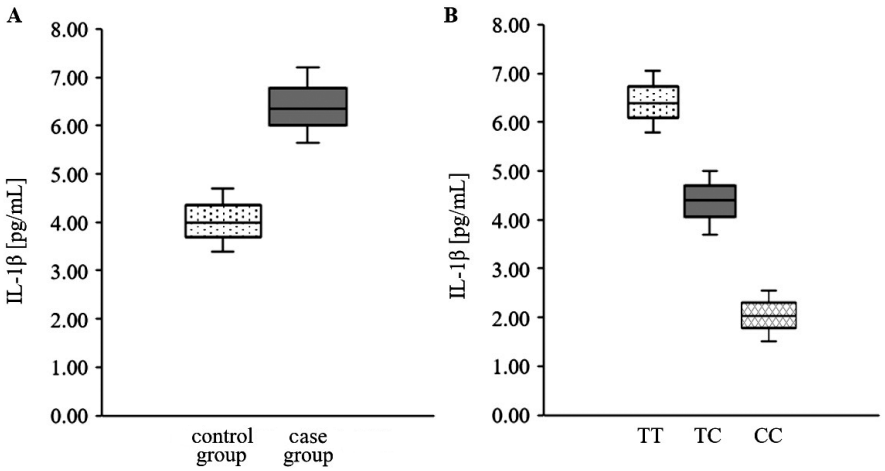

Fig. 1. Interleukin (IL)-1β levels in the case group and control group (A), and in different genotypes (B)

p = 0.008 for the control group compared to the case group; p = 0.011 for TT compared to TC; p = 0.002 for TT compared to CC; p = 0.005 for TC compared to CC.

gene cluster contains *IL-1B*, *IL-1A* and *IL-1RN* which are located on chromosome 2q. The *IL-1B*, encoding IL-1β, is demonstrated to be 7020 base pairs in length and contains numerous polymorphisms. Several SNPs within the promoter region of *IL-1B* have been researched in various infectious and inflammatory diseases.[35] Among them, the *IL-1B* polymorphism rs16944 has been correlated with IL-1β levels among rheumatoid arthritis patients in north India and hence affects disease susceptibility in which the T allele is directly associated with a higher IL-1β expression.[36] The CT genotype of *IL1B* rs16944 has also been shown to be associated with febrile seizure through the upregulation of postictal IL-1β levels in Korean children.[10] The AA genotype of *IL-1B* rs2853550 has been demonstrated to be correlated with a higher level of plasma IL-1β and, thus, an increased risk of ankylosing spondylitis.[37] In addition, the polymorphisms of rs10490571 (T/C) and rs1143623 (G/C) can also affect IL-1β levels in which the TC genotype of rs10490571 and the G allele of rs1143623 are associated with a higher level of IL-1β.[37,38] Therefore, multiple SNPs were included in our study.

According to the multivariate analysis, the *IL-1B* polymorphism rs16944 had an independent association with seizure susceptibility in ischemic stroke patients after adjusting for confounders. The TT and TC genotypes significantly increased the risk of post-stroke seizures compared to CC. We further compared IL-1β levels among different genotypes. The results showed that higher IL-1β levels were noted in TT compared to the TC genotype compared to the CC genotype. Therefore, the mechanism of the polymorphism of *IL-1B* rs16944 in affecting seizure susceptibility in ischemic stroke patients might be associated with the regulation of IL-1β levels.

Limitations

There were 2 main limitations to this study. The first was the small sample size, especially for the case group. Second, the study did not include all the SNPs associated with the expression of IL-1β.

Conclusions

The *IL-1B* polymorphism rs16944 had an independent association with seizure susceptibility in ischemic stroke patients. The mechanism for this might be associated with the regulation of IL-1β levels.

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