Serum level of IL-10 and IL-10-1082G/A polymorphism are associated with the risk of ischemic stroke: A meta-analysis

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Abstract

BACKGROUND

Stroke is one of the leading causes of disability and mortality among adults worldwide. The aim of the study was to confirm the relationship of serum interleukin-10 (IL-10) and its gene polymorphism with the risk of ischemic stroke (IS).

METHODS

PubMed and China Wanfang database were systematically searched up to September 2, 2019. Studies illustrating on the association between serum IL-10 or IL-10-1082G/A, IL-10-819C/T, IL-10- 592C/A polymorphisms and IS susceptibility were included in this study. Newcastle–Ottawa scale was used to assess the study quality. RevMan 5.3 was used for statistical analysis.

RESULTS:

Seventeen case-control studies were included in this meta-analysis which provides 3754 patients with IS and 5064 controls. Combined analysis indicated that patients with IS had lower serum level of IL-10 (Mean difference [MD]: -4.25; 95% confidence interval [CI]: -6.14 to -2.36, $p < 0.0001$). An association was identified between IL-10-1082G/A polymorphism and the risk of IS, but no association was found between polymorphism of IL-10-819C/T or IL-10- 592C/A and the risk of IS when all ethnic groups were considered together. For IL-10-1082G/A polymorphism, individuals with AA-genotype might have an increased risk of IS among Chinese Han population while no such correlation was observed in other ethnic group.

CONCLUSION

This meta-analysis suggested that low serum level of IL-10 and IL-10-1082G/A polymorphism may be associated with the risk of IS. More clinical studies should be conducted to confirm the relationship between serum IL-10 level and the risk of IS in all ethnic groups.

Background

Stroke is one of the leading causes of disability and mortality among adults worldwide, about 85% of stroke cases are ischemic, whereas 15% are hemorrhagic. Ischemic stroke (IS) is a focal neurologic deficit syndrome because of sudden occlusion of a cerebral artery by thrombus, causing ischemia cerebral hypoxia. Stroke mortality rate is high in developing countries, which accounts for two-thirds of stroke mortality worldwide[1]. It is estimated that the burden of IS will increase in the next 20 years with increasing number of older adults in developing countries.

IS can be attributed to both genetic and environmental factors, genetic susceptibility may be closely related to the development of IS. Interleukins 10(IL-10) as a key inflammatory cytokine plays a vital role in

various pathophysiological process[2]. There are lots of studies on the relationship between serum level of IL-10 or IL-10 gene polymorphism and the risk of ischemic stroke. Due to difference of sample size and region, the conclusion of research is controversial.

The objective of this meta-analysis was to investigate the association of serum level of IL-10 and several IL-10 gene polymorphism with the risk of IS.

Methods

This meta-analysis was executed according to the 2016 Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement[3].

Search Strategy

Eligible articles were searched by electronic database of PubMed and China Wanfang to up to September 2, 2019. The terms consist of Interleukin-10 and ischemic stroke.

Eligibility Criteria

Eligible studies must meet the following four criteria: 1) all studies should evaluate the relationship between serum level of IL-10, IL-10-1082A/G, IL-10-819C/T or IL-10-592C/A gene polymorphism and IS risk; 2) all studies had to be a case-control design; 3) all study cases should be diagnosed as ischemic stroke; 4) genotype distributions in both cases and controls were available to calculate an odds ratio (OR) with 95% confidence interval (CI); 5) Blood samples of ischemic stroke patients were collected at admission. Exclusion criteria: 1) Reviews, abstracts or animal studies. 2) study was not relevant to IL-10 serum level, gene polymorphism or IS; 3) study has no target outcomes.

Two investigators (Yeqin Sha and Xiaodong Rui) independently screened the articles. Eligible articles were included through reading the full text in detail.

Quality Assessment

Newcastle-Ottawa Scale[4] (NOS) was used to evaluate the quality of articles included. All seventeen studies were evaluated strictly and scored at least 6 points (Table 1).

Table 1
Quality Assessment of Included Studies According to the Newcastle–Ottawa Scale

Item/study	AD	RA	SCS	DCS	CIF	EA	SMA	NR	Total score
Xie[7]	1	0	1	1	2	1	1	1	8
Kes[8]	1	0	0	1	1	1	1	1	6
Singh[9]	1	0	0	1	1	1	1	1	6
Zhang[10]	1	0	1	1	0	1	1	1	6
Jin[11]	1	0	1	1	0	1	1	1	6
Li[12]	1	0	1	1	1	1	1	1	7
He[13]	1	0	1	1	1	1	1	1	7
Jiang[14]	1	0	0	1	1	1	1	1	6
Liu[15]	1	0	1	1	1	1	1	1	7
Tong[16]	1	0	1	1	1	1	1	1	7
Ozkan[17]	1	0	1	1	1	1	1	1	7
Munshi[18]	1	0	0	1	1	1	1	1	6
Kumar[19]	1	0	1	1	2	1	1	1	8
Sultana[20]	1	0	0	1	1	1	1	1	6
Belisário[21]	1	0	1	1	1	1	1	1	7
Marousi[22]	1	0	1	1	1	1	1	1	7
Tuttolomondo[23]	1	0	1	1	1	1	1	1	7
Note: Adequate definition of cases(AD); Representitiveness of cases(RA); Selection of control subjects(SCS); Definition of control subjects(DCS); Control for important factor or additional factor(CIF); Exposure assessment(EA); Same method of ascertainment for all subjects(SMA); Nonresponse rate(NR).									

Statistical analysis

Review Manager 5.3 (Cochrane IMS) was used for this meta-analysis. Random-effects model was conducted when heterogeneity is existing. Q-square test and the I^2 index was calculated to assess the heterogeneity, $I^2 \geq 50\%$ defined as significant heterogeneity. Hardy-Weinberg equilibrium (HWE) in the control group of articles included was examined by using Chi-square test. The dichotomous data of meta-analysis were reported as odds ratio (OR) and corresponding 95% confidence intervals (CIs). The mean difference (MD) and the associated 95% CI were calculated for continuous variables. In order to combine

results, the sample mean and standard deviation were estimated if the study reported median and interquartile range using the methods reported by Wan[5] and Luo[6].

Results

Retrieved studies

Based on our search strategy, 387 eligible studies were screened. The titles and abstracts of these studies were filtrated according to inclusion criteria. Finally, seventeen full text articles were eligible for this meta-analysis[7–23] (Fig. 1).

Study Characteristics

Three studies were included on the relationship between serum IL-10 level and ischemic stroke, including 274 patients. A total of fourteen studies which involved 3480 patients with IS were included to explore the relationship between IL-10-1082G/A polymorphism and the risk of IS. There are seven studies involving 1604 patients on the relationship between IL-10-819C/T polymorphism and the risk of IS. In addition, four studies were included to explore the association of IL-10-592C/A polymorphism with the risk of IS, involving 1040 patients.

Publication Bias

A comprehensive design was used in our study to minimize the publication bias. We have two researchers (Yeqin Sha and Xiaodong Rui) performed an intact search strategy and selected studies strictly according to the eligibility criteria and exclusion criteria. Finally, we used heterogeneity test to assess possible publication bias. In this system evaluation no evidence of publication bias was found.

Quantitative Synthesis

The results of this meta-analysis and heterogeneity test were shown in Table 2. We estimated the relationship between serum level of IL-10 or gene polymorphism and the risk of ischemic stroke with the dominant model and the recessive model.

Table 2
Association Between IL-10 Gene Polymorphisms and Ischemic Stroke

		Association			Heterogeneity	
Genetic model	Subgroup	OR (95% CI)	P	Effect model	I ² (%)	P _{het}
IL-10-1082G/A						
A vs. G	Overall	1.20(0.96–1.49)	0.11	R	78	0.000
	Chinese	1.30 (0.99–1.71)	0.06	R	63	0.01
	Other	1.11 (0.77–1.59)	0.58	R	86	0.000
AA vs. AG + GG	Overall	1.32 (1.02–1.70)	0.04	R	63	0.001
	Chinese	1.58 (1.15–2.17)	0.005	R	49	0.07
	Other	1.08 (0.72–1.60)	0.72	R	68	0.005
AA + AG vs. GG	Overall	1.23 (0.89–1.70)	0.34	R	71	0.000
	Chinese	1.46 (1.17–1.83)	0.001	R	0	0.64
	Other	1.10 (0.65–1.89)	0.72	R	83	0.000
IL-10-819C/T						
T vs. C	Overall	0.99 (0.89–1.11)	0.92	F	0	0.47
TT vs. TC + CC	Overall	0.95 (0.82–1.10)	0.51	F	0	0.57
TT + TC vs. CC	Overall	1.09 (0.88–1.35)	0.45	F	47	0.08
IL-10- 592C/A						
A vs. C	Overall	1.06 (0.93–1.21)	0.37	F	39	0.18
AA vs. AC + CC	Overall	1.15 (0.83–1.61)	0.40	R	54	0.09
AA + AC vs. CC	Overall	1.10 (0.84–1.44)	0.50	F	0	0.78
Note:OR, odds ratio; CI, confidence interval; F, fixed-effect model; R, random-effect model.						

Combined analysis indicated that patients with ischemic stroke had significantly lower serum level of IL-10 (Mean difference [MD]: -4.00; 95% confidence interval [CI]: -4.73 to -3.27, Fig. 2.). Funnel plot was implemented in this study and no substantial asymmetry was identified (Fig. 3).

The association between IL-10-1082G/A gene polymorphism and the risk of IS was then explored and significant heterogeneity was found among different ethnicities, therefore sub-group analysis was used. We conducted two subgroups, namely Chinese population and other ethnic groups. It demonstrated that significant association was observed between IL-10-1082G/A polymorphism and the risk of IS among

Chinese population (for AA vs. AG + GG: OR = 1.58, 95%CI:1.15–2.17, P = 0.005, Fig. 4) but for other ethnic groups (for AA vs. GA + GG: OR = 1.08, 95% CI: 0.72–1.60, P = 0.72, Fig. 4). Therefore, individuals with AA-genotype might have an increased risk of IS among Chinese Han population.

However, no association was found between polymorphism of IL-10-819C/T and IL-10- 592C/A (TT vs. TC + CC for IL-10-819C/T: OR = 0.95, 95% CI: 0.82–1.10, P = 0.51, Fig. 5; AA vs. AC + CC for IL-10-592C/A: OR = 1.15, 95% CI: 0.83–1.61, P = 0.40, Fig. 6) and the risk of IS among population.

Discussion

Our meta-analysis was the first study to show that lower serum level of IL-10 was closely associated with the risk of IS although the association of IL-10 gene polymorphism and the risk of IS had been explored before. We also confirmed that IL-10-1082G/A polymorphism had significant correlation with the risk of IS in Chinese Han population. Other ethnicities didn't show such association. In previous study, it is indicated that IL-10-1082G/A is associated with the risk of IS in Asian population, however, between-study heterogeneity is remarkable in their study[24]. Our study successfully solved the high heterogeneity by subgroup analysis, finding significant correlation between IL-10-1082G/A polymorphism and the risk of IS among Chinese population. However, the heterogeneity in subgroup of other ethnic groups was still high, due to small sample size, different regions and limited number of case-control studies.

Furthermore, our meta-analysis examined other common gene polymorphisms of IL-10 promoter region such as IL-10-819C/T and IL-10-592C/A and showed no correlation with the risk of IS. Considering the limited number of case-control studies exploring the correlation between IL-10-819C/T and IL-10-592C/A polymorphism and the risk of IS, more studies is needed to clarify its association. Therefore, our result suggested that IL-10-1082G/A may be the only one which is associated with IS susceptibility.

Despite of the strict retrieval, statistical quality control, publication bias test mentioned above, the current study still has some limitations that should be addressed. In the future, we need more high-quality study which involves more ethnic and regional population, makes a comprehensive evaluation of relationship between serum level of IL-10 or IL-10 gene polymorphism and the risk of IS.

Conclusion

This meta-analysis suggested that the lower serum level of IL-10 was closely related to high risk of IS. IL-10-1082G/A polymorphism may be associated with the risk of IS in Chinese population. More clinical studies should be conducted to confirm the relationship between the serum level of IL-10 and the risk of IS and the relationship between lower serum level of IL-10 and IL-10 promotor gene polymorphism can be explored further.

Declarations

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Figures

Figure 2

Flowchart for screening articles eligible

Figure 4

Forest plot for the relationship between ischemic stroke and serum IL-10 level

Figure 6

Funnel plot for the relationship between ischemic stroke and serum IL-10 level

Figure 7

Forest plot for the relationship between IL-10-1082G/A polymorphism and the risk of IS

Figure 9

Forest plot for the relationship between IL-10-819C/T polymorphism and the risk of IS

Figure 12

Forest plot for the relationship between IL-10- 592C/A polymorphism and the risk of I