Association of Interleukin-10 (Il-10) Serum Levels with Clinical Outcomes of Acute Ischemic Stroke Patients

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ORIGINAL ARTICLE

Association of Interleukin-10 (Il-10) Serum Levels with Clinical Outcomes of Acute Ischemic Stroke Patients

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ABSTRACT

Background: The pathophysiology of ischemic stroke is closely related to the inflammatory response that directly proportional to brain tissue damage. Interleukin-10 (IL-10) is an important anti-inflammatory cytokine that arises in response to brain injury.
Aim: To determine the association of serum IL-10 levels with clinical outcomes of acute ischemic stroke patients.
Method: An analytical observational study with prospective cohort designs included 48 subjects of first acute ischemic stroke. On 3rd and 21stday of onset, scores of national institutes of health stroke scale (NIHSS) were assessed and venous blood was taken to measure IL-10 serum levels.
Result: Among 48 subjects, 32 (66.67%) subjects had high IL-10 serum level and 16 (33.3%) had normal level. There were no significant relationships between age (p=1.000), sex (p=0.833), type of lesion (p=0.683), ECG (p=0.230), nutritional status (p=0.186), hypertension (p=0.215), diabetes mellitus (p=0.130), dyslipidemia (p=0.383), smoking status (p=0.654) and NIHSS score.The multivariate analysis obtained significant correlation between interleukin (IL)-10 (p=0.023, OR=5.456), location of non-dominant hemispheric lesions (p=0.024, OR=5.090) with NIHSS score changes.
Conclusion: There was significant association between IL-10 serum levels, location of non dominant hemispheric lesion andan improvement of clinical outcomes of acute ischemic stroke patients.
Keywords: Interleukin-10 serum levels,acute ischemicstroke;clinical outcomes of acute ischemic stroke patients

INTRODUCTION

Stroke is the third leading cause of death worldwide, as well as being a major cause of disability especially in developing countries.[1] The occurrence of ischemic stroke is more common than hemorrhage strokes, approximately 80-85% of all stroke events.[2] The pathophysiology of ischemic stroke is thought to be related to the inflammatory response. Interleukin-10 (IL-10) is an important anti-inflammatory cytokine that arises in response to brain injury. IL-10 facilitates the resolution of inflammatory cascades, which, when prolonged, leads to secondary brain damage.[3] The role of IL-10 in clinical outcomes of ischemic stroke is controversial. Some evidence suggests that cerebral IL-10 expression is useful in post stroke, since IL-10 overexpressing IL-10 transgenic mice on astrocytes, microglia, and endothelial brain cells indicate a smaller infarction.[4]The aim of this study is to prove the relationship between immunological response and clinical outcomes of an acute ischemic stroke patient. The immunological response was seen from the peripheral circulating IL-10 levels, whereas the clinical outputs of ischemic stroke was measured by NIHSS score.

MATERIALS AND METHODS

The research was an analytical observational study with prospective cohort designsconducted in dr. Kariadi and dr Soesilo hospital both inpatient and outpatient units. The subjects were acute ischemic stroke patients with first onset <72 hours proven by a CT scan of the plain head and agreed to participate. The patients who had an infection when admitted, had ischemic stroke with malignancy, had a history of moderate / severe head injury <3 monthsand an acute myocardial infarction 3 weeks before onset of stroke, hadpsychiatric disorders, had done rTPa, were pregnant, and had a historytaking of steroid or immunosuppressant drugs, wereexcluded from this study. Patients who died before 21st day of onset, developed an infection or being discharged between 3rd and 21st day of onset were dropped out of this study.

The subjects were then measured the NIHSS scores and taken their venous blood sampleson the 3rd day onset of ischemic stroke as many as 5 cc of frozen blood without EDTA to check serum IL-10 levels. During treatment, the subjects obtained standard stroke therapy such as anti-platelet, anti-hypertension, and neurotropic. After 21st day onset, patients were remeasured NIHSS score.
Statistical Analysis: Statistical analysis included descriptive, bivariate and multivariateanalysis. Descriptive analysis describedthe characteristics of the subjects. Chi-square and fisher exact test were used to test the relationship between variables while multiple regression logistic test was used to know the contribution of confounding variables. The p value was considered significant if $p < 0.05$.
Research Ethics: Prior to the research, the authors applied for ethical clearance from the Medical Research Ethics Committee, Faculty of Medicine,Diponegoro University / dr.Kariadi hospital. Family approvals were requested in the form of written informed consent. Patients or families had the right to refuse to be included in the study without any consequences. The identities of the patient were kept confidential.

RESULT

This study recruited 48 subjects who met inclusion and exclusion criteria. Table 1 shows the characteristics of subjects. The majority of respondents were male

(28;58.3%), adult (37;77.1%), normoweight (46;95.8%), having normosinus rhythm (34;70.8%), no smoking (38;79.2%), dyslipidemia (24;50%), did not have diabetes mellitus (35;72.9%); having hypertension (41;85.4%), having non dominant hemispheric lesion (27;56.2%), and had lacunar lesion type (42;87.5%). The result showed that 32 (66.7%) subjects had high IL-10 serum levelsand 16 (33.3%) subjects had normal IL-10 serum levels. On the other hand, 27(56.2%) subjects had improved NIHSS while 21 subjects had fixed NIHSS score (43.8%) as can be seen in table 2.

Bivariate analyses showed that age (p=1.000), sex (p=0.833), type of lesion (p=0.683), ECG (p=0.230), nutritional status (p=0.186), hypertension (p=0.215), diabetes mellitus (p=0.130), dyslipidemia (p=0.383) and smoking status (p=0.654) were not significantly correlated with the NIHSS score. However, there was a significant correlation between the location of ischemic (p=0.025), IL-10 levels(p=0.014) and NIHSS score changes.(Table 3)

Multivariate analysis obtainedinsignificant correlation between hypertension (p=0.133; OR=0.218), diabetes mellitus (p=0.920; OR=3.913) and NIHSS score while interleukin-10 level (p=0.023, OR=5.456) and location of non-dominant hemispheric lesion (p=0.024, OR=5.090) had significant correlation with NIHSS score changes.(Table 3)

Table 1: Statistical Analytic of Confounding Variables

Subject Characteristics	NIHSS Changes				Statistical Analysis	P
	Improve		Fixed			
	N	%	n	%		
Gender						
Man	16	59.3	12	57.1	X^2=0.022	0.883§
Woman	11	40.7	9	42.9		
Age						
Elderly	6	22.2	5	23.8	X^2=0.017	1.000¥
Adult	21	77.8	16	76.2		
BMI						
Non obesity	27	100	19	90.5	X^2=2.683	0.186¥
Obesity	0	0	2	9.5		
ECG						
NSR	21	77.8	13	61.9	X^2=1.441	0.230§
LVH	6	22.2	8	38.1		
Location of Ischemic						
Non dominant Hemisphere	19	70.4	8	38.1	X^2=5.000	0.025§*
Dominant Hemisphere	8	29.6	13	61.9		
Type of Lesion						
Single territorial	4	14.8	2	9.5	X^2=0.302	0.683¥
Lacunar	23	85.2	19	90.5		
DM						
Yes	5	18.5	8	38.1	X^2=2.292	0.130§
No	22	81.5	13	61.9		
Dyslipidemia						
Yes	12	44.4	12	57.1	X^2=0.762	0.383§
No	15	55.6	9	42.9		
Hypertension						
Yes	25	92.6	16	76.2	X^2=2.551	0.215¥
No	2	7.4	5	23.8		
Smoking status						
Yes	5	18.5	5	23.8	X^2=0.210	0.654§
No	22	81.5	16	76.2		

Abreviation : * Significant; ¥ Fisher's Exact; § Pearson chi square;

Table 2: Chi-Square Test between IL-10 serum levels with NIHSS score changes

IL-10 serum levels	NIHSS score changes				P
	Improve		Fixed		
	N	%	N	%	
High	22	81.8	10	47.6	0.014§
Normal	5	18.5	11	52.4	

Abreviation : § Pearson chi square

Table 3: Multivariate Analysis by using Logistic Regression

Variable	NIHSS Changes		Bivariate				Multivariate			
	Improve	Fixed	*p value*	*OR*	CI 95		*p value*	*OR(EXP(B))*	CI 95	
	N	N			Min	max			Min	max
Gender										
Man	16	12	0.89	1.09	0.34	3.47				
Woman	11	9								
BMI										
Non obesity	0	2	0.19	0.42	0.29	0.54				
Obesity	27	19								
ECG										
NSR	21	13	0.23	0.47	0.13	1.64	0.125	3.60	0.70	18,51
LVH	6	8								
Hypertension										
Yes	25	16	0.22	0.26	0.04	1.48	0.133	0.22	0.03	1.59
No	2	5								
Type of Lesion										
Single Territorial	4	2	0.68	0.61	0.10	3.67				
Lacunar	23	19								
Ischemic location										
Non dominant										
Hemisphere	19	8	0.03	3.86	1.15	12.9	0.024	5.09	1.24	20.93
Dominant Hemisphere	8	13								
DM										
Yes	5	8	0.13	2.71	0.73	10.1	0.92	3.91	0.80	19.12
No	22	13								
Dyslipidemia										
Yes	12	12	0.38	1.68	0.53	5.27				
No	15	9								
IL-10 serum levels										
High	22	10			1.33	17.7	0.02	5.46	1.27	
Normal	5	11	0.03	4.84						23.53

DISCUSSION

The pathophysiology of ischemic stroke involves a complex inflammatory response, ranging from the process of thrombosis or embolism that causes the death of neuronal cells in the brain parenchyma.[1] Neuronal death is caused by an ischemic cascade consisting of glutamate exotoxicity, intracellular calcium overload, free radical toxicity, and inflammation of cerebral parenchyma[5]. The inflammatory response to ischemic stroke begins from a process of atherosclerosis before the onset of stroke.[6]Cytokines become the medium of communication between immune cells in activating or suppressing inflammatory responses. Proinflammatory cytokines such as IL-1β, TNF-α, and anti-inflammatory cytokines are IL-10, TGF-β.[4,7-9]

Interleukin-10 (IL-10) is an important anti-inflammatory cytokine expressed in response to brain injury, where it facilitates the resolution of inflammatory cascades, which if prolonged causes secondary brain damage.[3]It has been estimated that elevated levels of IL-10 have neuroprotective function. Higher levels of IL-10 serum suggest a tissue after an ischemic stroke. In addition, the number of peripheral blood mononuclear cells (PBMC) that secrete IL-10 increases in patients with ischemic stroke and cerebral hemorrhage.[10]Previous study, found a significant correlation between IL-10 expression levels and neurological improvement.[11]In our study, we found a significant correlation between IL-10 serum levels and NIHSS score changes. It had inverted correlation, higher IL-10 serum levels had more improvement to clinical outcomes of ischemic stroke. IL-10 provides a negative feedback mechanism by blocking the monocytes/ macrophage gene transcription to limit the production of proinflammatory cytokines, IL-6 and TNF-a, intercellular adhesion molecule-1 (ICAM-1), and matrix metalloproteinase (MMP)[11].

Previous research on side of lesion has yielded contradictory results. Despite reviews that found no differences in outcome between dominant and non dominant cerebral lesions.[12]Our study supports findings obtained by other researchers who found significant correlation between location of lesion with NIHSS score changes. Non dominant hemispheric lesion had more improvement in clinical outcome of ischemic stroke patients. However, it was mentioned that infarct lesions in dominant hemispheres tend to produce worse clinical outcomes, as well as a heavier degree of stroke.[13]In this study, majority patient used left hemisphere as their dominant hemisphere. Based on previous study, on right hemisphere they identified the parietal lobe and putamen as key areas associated with unfavorable outcomes. The right parietal lobe is a complex structure with a rich array of functions including the primary somatosensory cortex (postcentral gyrus), as well as areas critical for somatosensory association and visuospatial function. The putamen is part of the striatum with important cortical and sub-cortical connections that predominantly mediate motor function[14].

In the left hemisphere, the primary areas of importance identified in the tree were the uncinate fasciculus, precuneus, and angular gyrus. The uncinate fasciculus connects the orbitofrontal and anterior temporal cortex and is traditionally understood to be a limbic structure with proposed functions including episodic

memory, language (left-hemisphere), and social and emotional processing.[15,16]The precuneus is a medial parietal structure that has extensive cortical and sub-cortical interconnections and has been implicated in a range of higher order functions including consciousness, visuospatial imagery, episodic memory retrieval, and self-processing.[17] It has been identified as one of the primary brain areas demonstrating task-independent decreases in activation on functional imaging and is one of the most metabolically active brain regions during rest, being one of the principal components of the default-mode network.[18] The left angular gyrus, along with Wernicke's area (part of the superior temporal gyrus), the supramarginalgyrus, and parts of the middle temporal gyrus, form the posterior language area. It has important roles in language comprehension and arithmetic retrieval.[14,19]Specific infarct patterns are related to cerebral arterial occlusion mechanisms and are correlated with functional outcome. Otherwise, the results of a study indicates that infarct patterns on diffuse weighted imaging (DWI) might be a clue for determining ischemic stroke etiology on patients with major cerebral artery occlusion. In this study we found insignificant correlation between type of lesion (lacunar lesion and territorial lesion) with clinical outcomes. The degree of stroke severity is determined by the extent of the lesion, where the lacunar lesion is milder clinically compared to the territorial type, and these findings are consistent with several studies that suggest lacunar infarcts are most commonly found in either solitary or multiple.[5]

Previous study showed that gender factors did not affect the clinical outcome of acute ischemic stroke. This study also had insignificant correlation between gender and improvement of NIHSS score changes. Some authors have shown that increased age predicts poor outcome after stroke.[20]In this study, we did not notice this correlation between age and NIHSS changes, however we found insignificant correlation that same as other researchers which maintain that age is not an independent predictor of functional outcome.[21] Some studies suggest that hypertension is a risk factor for ischemic stroke. In this study there was no association between hypertension and the NIHSS score because hypertension is not the only independent predictor of clinical outcomes of ischemic stroke. Comorbid medical disorders (hypertension, diabetes, cardiac disease) were not found to be significantly related to functional outcome.[1]Wealso found hypertension, diabetic mellitus, past medical history, electrocardiography examination did not correlate to clinical outcomes of acute ischemic stroke.

Several modifiable and non-modifiable factors such as smoking, hyperlipidemia, obesity, sedentary lifestyle, cardiac abnormalities (e.g. arterial fibrillation), age, and sex have been reported to increase the risk of acute ischemic stroke (AIS).[22]Dyslipidemia is a major risk factor for coronary heart disease (CHD) and its role in the pathogenesis of ischemic stroke is still unclear.[23]Serum levels of TC, LDL-C, and HDL-C are positively related with the outcome in patients with acute ischemic stroke.[24]This study showed insignificant correlation between body mass index (BMI), dyslipidemia, and smoking status. This is probably due to the lack of specific categories in this study.

CONCLUSION

The finding concluded that there was a significant association between IL-10 serum levels and location of non-dominant hemispheric lesion with clinical outcome improvement of acute ischemic stroke patients.

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