Ischemic stroke

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Original Article

Comparing Level of 4HNE in Acute Phase of Ischemic Stroke patients and its Association with Cognitive Function After Stroke Event

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Abstract

Background: Stroke is the leading cause of disability in the productive age, not only because of physical disability, but also due to impaired cognitive function following a stroke event. Brain damage-related stroke can be triggered by increasing the level of free radicals. 4HNE is the main and most toxic product that is released from free radical attack on polyunsaturated fatty acids.
Objectives: To determine plasma level of 4HNE in patients recovering from acute phase of stroke and these with normal subjects and calculate its relationship with cognitive function after 3 months of stroke event.
Patients and Methods: Eighty four patients suffering from ischemic stroke and 42 normal subjects (controls) were studied. In patients plasma 4HNE was measured between 24-72 hours of stroke and cognitive function was examined using MoCA-Ina after 3 months of stroke.
Results: Plasma 4HNE was 2.5-fold increased in patients than controls ($p < 0.05$). The elevation was found in patients having cognitive impairment as compared to those who did not have cognitive impairment, but this was not statistically significant and no relationship was found between plasma 4HNE level and cognitive impairment after stroke. Cognitive impairment at three months after stroke was found in 56% cases.
Conclusion: Elevation of plasma 4HNE was seen in acute phase of stroke but it was not associated with impaired cognitive function after 3 months of stroke event.
Key words: 4HNE, cognitive function, ischemic stroke.

Introduction

Stroke is the third leading cause of death and disability in the productive age and it not only decreases the quality of life, due to physical disability, but also leads to decrease or impairment of cognitive functions after a stroke event[1].

Brain damage-related stroke is also triggered by the presence of oxidative stress apart from the disruption of blood flow[2]. Under normal circumstances, there is a balance between pro-oxidant and anti-oxidant, but in certain conditions, such as reduced blood flow (oligomia), this balance is disrupted leading to increased production of free radical[3]. The brain is most easily exposed to oxidative processes, because it consists of high unsaturated fatty acids so it needs lot of oxygen, high levels of transition metal ions and low levels of antioxidant[4]. Free radicals attack the phospholipids of Polyunsaturated fatty acids (PUFAs) and produce a variety of aldehydes with different carbon chain lengths, such as malondialdehyde (MDA), acrolen and 4HNE.

4HNE is an α, β unsaturated aldehydes, which easily binds with various amino acid residues such as histidine, lysine and cysteine and produces effects such as inhibiting the transport of glucose, glutamate, Na-K-ATPase, activating kinase and disrupting regulation of calcium signaling cascade that stimulates apoptosis[5]. 4HNE is a major and the most toxic product of free radical attack on PUFA, because it can lead to impaired function of membrane proteins, including glucose transport in neurons[6]. 4HNE are very good at diffusion and is distributed away from its production place[7]. Level of free 4HNE is increased in different areas of brain and ventricular cerebrospinal fluid in patients with dementia[8] and is chemically more reactive and therefore is more damaging to lipid membranes[6]. One worker reported that 4HNE causes neuronal apoptosis and this effect was not

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seen in the other aldehydes[9]. While another worker studied 29 subjects with suspected Alzheimer's Disease and reported that 4HNE elevation was found associated with the degree of cognitive impairment but not in *malondialdehyde* (MDA)[10].

Oxidative stress causes interference to brain cells through two mechanisms that cause changes in the brain tissue. Firstly, it decreases the neurotransmitter that is needed in the communication between nerve cells in the brain. Secondly, it reduces the amount of anti-oxidants needed to neutralize free radicals substances. Four Hydroxinonenal decreases the acetylcholine transferase activity, by binding to the active site of histidine and finally disrupting its activities[11,12]. Neurotransmitters must be available in balance to maintain normal function and behavior.

Patients and Methods

A total of 84 ischemic stroke patients were enrolled from the Neurology Ward of Djamil hospital in Padang Indonesia, from March to September 30th 2013. Patients between the ages of 40-78 years who were hospitalized within 6-72 hours after the onset of first-ever ischemic stroke, affecting carotid or vertebrobasilar system were enrolled. The diagnosis was clinically established by monitoring trends and determinants of cardiovascular disease. Patients were excluded if they had any history of cognitive impairment before stroke, hemorrhagic stroke, dysarthria or severe aphasia, impaired consciousness and depression.

Forty-two healthy subjects matched with age, education and gender were also included as controls. The control group did not suffer a stroke, hypertension, heart disease, diabetes and other neurological/psychiatric disorder.

Neurological deficit was assessed using National Institutes of Health Stroke Scale (NIHSS) scores. Blood samples were taken in the fasting state between 6-72 hours of the onset of stroke and placed in vacutab EDTA tube. 4HNE level in the blood was measured by a commercial kits double-sandwich enzyme-linked immunosorbent assay (ELISA) (Cell Biolabs Inc., STA-338. (888) CBL - 0505) according to the manufacturer's instructions.

Cognitive assessment was performed after 3 months of the onset of stroke for patients and immediate after the blood collection in controls using Montreal Cognitive Assesment-Indonesian version (MoCA-Ina). The Moca-Ina had been validated in the local population.

Based on the results of MoCA-Ina, the study group was divided into

1. Patients with cognitive impairment
2. Patients with normal cognitive function
3. The control group

All statistical calculations were performed using computerized software. Data were presented as median (min - max). Differences between groups were analyzed with the Kruskal-Wallis test with post hoc Mann-Whitney test. The association between variables were analyzed using chi-square and considered significant if $p < 0.05$.

Results

Eighty-four patients were enrolled in this study with 47 (55.9%) having cognitive impairment and 37 (44.1%) without cognitive impairment. Forty-two healthy subjects served as controls. No significant difference was noted regarding age, gender and education, between the patients and controls ($p > 0.05$) (Table-1).

Table 1 Basic Characteristics of cases group and controls group.

Basic Characteristics	*Subjects Research*		*p*
	Cases (n = 84)	*Controls (n = 42)*	
Age	60.50 ± 9586	60.50 ± 6.73	0.994
Gender: Male / Female	41/43	20/22	0.295
Education: Low / High	56/28	24/18	0.794
Hypertension	77/84 (91.66%)	-	-
Diabetes Mellitus	13/84 (15.48%)	-	-
Dyslipidemia	59/84 (70.24%)	-	-
Smoking	19/84 (22.62)	-	-

As shown in Table-2, cognitive impairment were more common in patients (55.9%) than controls (16.7%) and this difference was statistically significant ($p < 0.001$ and OR value of 6.667).

Table 2. Distribution of cognitive disorders in the case group and control group.

	Impaired Cognitive Function		*Normal Cognitive Function*		*p*	*OR*
	n	*%*	*n*	*%*		
Case group	48	55.9	36	44.1	< 0.001	6.667
Control group	7	20.6	35	79.4		

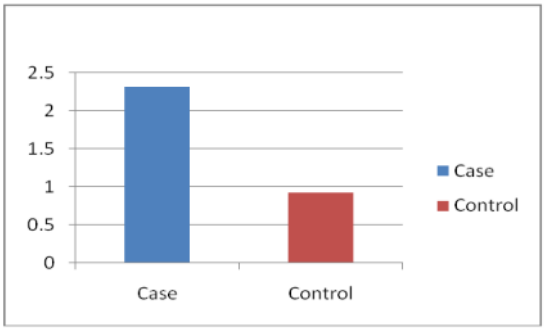

Figure: Plasma levels of 4HNE.

Table 3: Plasma levels of 4HNE in the case and control groups.

Variables	*Group*	*n*	*Median (Min - max)*	*Mean ± SD*	*p*
4HNE	Cases of impaired cognitive function	48	2.30282(2,185-2.6)	2.30282±.094336	
	Cases without impaired cognitive function	36	2.3289(2.23 to 2.69)	2.3289 ±.10359	< 0.001
	Control	42	0.919 (0.90 to 0.945)	0.919 ± 0.008	

Kruskal Wallis. Post-hoc Mann Whitney test for impaired cognitive case vs normal, $p = 0.191$, impaired cognitive cases vs. controls $p < 0.001$

Plasma level of 4HNE in patients with cognitive impairment and without cognitive impairment and controls are shown in Figure. The levels of 4HNE were elevated in patients as compared to control and this was statistically significant ($p < 0.001$).

The association between plasma levels of 4HNE in each group is shown Table-3 using Kruskal-Wallis test and post hoc Mann-Whitney test. Significant differences were found between plasma 4HNE levels of patients having cognitive impairment as compared to the controls ($p < 0.001$) but no significant association was found between plasma levels of 4HNE in patients with cognitive impairment as compared to those without cognitive impairment ($p > 0.191$).

To assess the association between plasma levels of 4HNE with cognitive function in the patients, the cutoff point was determined using Receiver Operating Characteristic procedure (ROC), and the optimal cut off point was 2.24. Based on this value, the plasma levels of 4HNE was considered 'high' when the value was > 2.24 and 'low' when the value was ≤ 2.24. Table-4 shows the association between plasma level of 4HNE and cognitive function.

Table 4: The Association of blood levels of 4HNE and impaired cognitive function in patients after ischemic stroke.

4HNE levels		*Cognitive Function*		Total
		Impaired	*Normal*	
High	N	24	12	36
	%	48.9	35.1	42.9
Low	N	24	24	48
	%	51.1	64.9	57.1
Total	N	48	36	84
	%	100.0	100.0	100.0

$p > 0.05$ (p-value = 0.204) Odds Ratio = 1.769
(95% CI = 0.730 to 4.285)

No statistically significant association was found between plasma levels of 4HNE with impaired cognitive function (p = 0.204 and OR 1.769) meaning that the groups with high levels of 4HNE is at 1,769 times higher risk for cognitive impairment than the group with low levels of 4HNE.

Discussion

The results of this study indicate that cognitive impairments are found more in patients than controls. Incidence of cognitive impairment after stroke was 55.9% which is higher than that reported by Haring who suggested that 25% of stroke patients develop dementia after 3 months post-stroke[13]. Another worker reported 23-55% incidence of dementia in post stroke (PSD) cases whether a first-ever stroke or recurrent stroke[14]. Khedr reported PSD in 21% which was inversely proportional to age and education levels[15].

Elevation of plasma, levels of 4HNE in the acute phase of stroke as reported in this study are similar to the findings of others[16,17]. Four hydroxinonenal is now suspected as a potential biomarker for ischemic stroke and is positively associated with plasma homocysteine levels[18].

In the present study, plasma level of 4HNE was higher in patients having cognitive impairment as compared to those without cognitive impairment. Another worker studied patients with suspected Alzheimer's disease and reported that 4HNE elevation was associated with the degree of cognitive impairment but it was not found in *malondialdehyde* (MDA)[10].

Elevation of 4HNE levels was found in all cases after stroke but this rise was not seen after stroke in the present study. Min Guo also found 3 times elevated levels of 4HNE in acute phase of stroke as compared to nonstroke subjects and showed the severity of the oxidative stress that occurs in the process of cerebral infarction (stroke)[19].

Present study has several shortcomings. First, the study was conducted only at one hospital. While multicentre cohort study with a larger number of cases is needed. Second, this study only compared stroke patient with the normal population but not compared patients who have vascular risk factors but have not had a stroke. Larger studies will solve further querries or sustantiate these findings.

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