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The Correlation of Glial Fibrillary Acid Protein Level to Cognitive Function Outcome in Acute Lacunar Ischemic Stroke Patient

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Abstract

AIM: Glial fibrillary acidic protein (GFAP) is a filamentous protein found in central nervous system astrocytes. Increased serum GFAP levels are caused by the process of astrogliosis after ischemic stroke and are associated with multisynaptic disorders so that they are at risk of causing cognitive disorders.

OBJECTIVE: The aim of the study was to analyze the correlation between GFAP levels and cognitive function output in acute lacunar ischemic stroke patients.

RESEARCH METHODS: This was a znalytical observational with prospective and cohort approach. The subjects of this study were acute lacunar ischemic stroke patients with mild-to-moderate NIHSS scores. Serum GFAP levels were taken at the onset of 48–72 h of stroke. Cognitive function was measured using the Indonesian version of MoCA (MoCA Ina) test on the 7th and 30th day. Bivariate and multivariate analyzes were performed to assess the correlation between GFAP levels, cognitive functions, and the confounding factors.

RESULTS: There was a significant correlation between GFAP levels and the MoCA Ina scores on the 7th day ($r = -0.32$, $p = 0.044$), the 30th day ($r = -0.398$, $p = 0.011$), and improvement in MoCA Ina scores ($r = -0.342$, $p = 0.031$). There was a significant correlation between GFAP levels on the executive domain on the 7th day ($p = 0.01$) and 30th day ($p = 0.005$), visuospatial on 7th day ($p = 0.004$) and 30th day ($p = 0.016$), language on the 30th day ($p = 0.005$), and memory on 30th day ($p = 0.001$). There was no significant correlation between GFAP levels and improvements in attentional, memory, language, visuospatial, and executive domains.

CONCLUSION: There was a significant correlation between GFAP levels and MoCA Ina scores on the 7th, 30th day and the improvement of MoCA Ina scores. There was a significant correlation between GFAP levels with the executive, visuospatial, language, and memory domains.

Introduction

Ischemic stroke is a group of symptoms caused by an acute disturbance of brain function (neurologic deficit), both focal or global, sudden, lasts more than 24 h, and is caused by reduced or lost blood flow in the parenchyma of the brain, retina, or spinal cord, which can be caused by blockage of arteries or veins as evidenced by brain imaging studies and/or pathology. A report from the American Heart Association states that ischemic stroke accounts for 87% of all strokes, and the rest are hemorrhagic strokes and subarachnoid hemorrhage [1], [2], [3], [4], [5].

Stroke patients will be at higher risk of experiencing cognitive impairment. Stroke is the second most common cause of dementia. The incidence of cognitive deficits increases threefold after stroke, and approximately 25% of stroke patients develop dementia. Post-stroke cognitive impairment (PSCI) is defined as cognitive and neurological deficits that develop up to the 3rd month after stroke with a minimum duration of 6 months and are not associated with other conditions or diseases such as metabolic and endocrine disorders, vasculitis, and depression. The disorder is classified into non-dementia cognitive disorder and dementia cognitive disorder when the performance of daily social activities and functions is disturbed [6], [7], [8], [9], [10].

A stroke will result in damage to glial cells, which is characterized by increased serum levels of glial fibrillary acid protein (GFAP). GFAP is an intermediate filament III protein found in central nervous system (CNS) astrocytes. Increased serum GFAP levels are caused by the process of astrogliosis after ischemic stroke and are associated with multisynaptic disorders, so there is a risk of causing cognitive impairment [11], [12], [13], [14], [15]. The purpose of this study was to analyze the relationship between GFAP levels and cognitive function output in acute lacunar ischemic stroke patients.

Methods

This research is an analytical and observational study with a prospective and cohort approach. Subjects

Table 1: The demographic characteristics of subjects

Variable	F	%	Mean ± SD	Median (min–max)
Age			58.83 ± 9.60	60.5 (36–75)
≥65 years	10	25		
<65 years	30	75		
Gender				
Male	26	65		
Female	14	35		
Education				
<12 years	12	30		
>12 years	28	70		
Work				
Not work	13	32.5		
Working	27	67.5		

Table 2: Clinical characteristics of research subjects

Variable	F	%
Hypertension		
Yes	35	87.5
No	5	12.5
DM		
Yes	11	27.5
No	29	72.5
Dyslipidemia		
Yes	38	95
No	2	5
Obesity		
Yes	7	17.5
No	33	82.5
Number of lacunar infarcts		
Multiple	32	80
Single	8	20
Location of lacunar infarction		
Strategic	19	47.5
Non-strategic	21	52.5
History of stroke		
Repeated strokes	9	22.5
First stroke	31	77.5

with acute lacunar ischemic stroke with mild-to-moderate NIHSS scores that came before 72 h of onset. The exclusion criteria in this study were subjects in the absence of consciousness disorders, both qualitative and quantitative, no previous cognitive impairments, no aphasia, and other neuropsychiatric disorders such as brain infections, head trauma, autoimmune disorders, and brain tumors. A total of forty acute lacunar ischemic stroke patients were assessed for GFAP levels at the onset of 48–72 h of stroke. Cognitive function was measured by Indonesian version of MoCA (MoCA Ina's) score on the 7th and 30th days. Bivariate and multivariate analysis was carried out to assess the relationship of GFAP with cognitive function along with influencing factors such as age, gender, education, occupation, hypertension, diabetes mellitus, dyslipidemia, obesity, stroke history, infarction location, and number of lesions.

Results

According to the demographic data based on Table 1, the sample is dominated by subjects with aged <65 years (30%), male sex of 26 subjects (65%), education >12 years of 28 subjects (70%), and there were 27 working subjects (67.5%).

Clinical characteristics (Table 2) were dominated by 35 subjects (87.5%) with hypertension, 29 subjects (72.5%) without diabetes, 38 subjects (95%) with dyslipidemia, and 33 subjects (82.5%) who were not obese. Other clinical data features include infarct size, where the infarct strategy location (left angular gyrus, temporal inferomesial, frontal mesial, thalamus, genu internal capsule, and caudate nucleus) was obtained in 19 subjects (47.5%) with strategic locations and 21 non-strategic subjects (52.5%), the number of infarct lesions found was 32 multiple lesions (80%) and 8 single lesions (20%), and recurrent strokes were found in 9 subjects (22.5%) and the first stroke was obtained in 31 subjects (77.5%).

Table 3 shows that the average GFAP level until the onset of 72 h is 2.26 ± 1.53, with a median of 1.93. The 7th day onset MoCA Ina score was 25.23 ± 2.37 with a median of 26, and the 30th day onset MoCA Ina score was 26.75 ± 2.48 with a median of 27.00.

Table 3: Characteristics of GFAP and MoCA Ina levels

Variable	Average (sb)	IK95%	Median (Minimum–Maximum)
GFAP	2.26 (1.53)	1.76–2.74	1.93 (0.25–6.76)
MoCA Ina D7	2 5,23 (2, 37)	24.47–25.98	26 (1 7–30)
MoCA Ina D30	2 6.75 (2.48)	25.95–27.55	2 7 0.00 (1 7–30)
Improvements to MoCA Ina	1.53 (0.68)	1.31–1.74	2.00 (0–2)

In Table 4, it can be concluded that the relationship between GFAP levels and MoCA Ina onset on the 7th day obtained a significant correlation (p = 0.044) with a weak correlation strength (r = −0.32) and a negative correlation direction where the higher the GFAP value, the lower the score for MoCA Ina on the 7th day. The relationship between GFAP levels and MoCA Ina at the onset of the 30th day obtained a significant correlation (p = 0.011) with a weak correlation strength (r = −0.398) and a negative correlation direction, the higher the GFAP value, the lower the MoCA Ina score on the 30th day. There was a significant correlation (p = 0.031) with a weak correlation strength (r = −0.342) and a negative correlation direction, the higher the GFAP value, the more inhibited the improvement of Ina's MoCA score between the 7th and 30th days.

Table 4: Relationship between GFAP levels and MoCA Ina

Variable	MoCA Ina D7		MoCA Ina D30		Improvements to MoCA Ina	
	p	r	P	r	p	r
GFAP	0.044	−0.32	0.011	−0.398	0.031	−0.342

Spearman correlation test.

Significant results were obtained between the GFAP values at the onset of the 3rd day and impaired executive (p = 0.01) and visuospatial (p = 0.004) on the 7th day of onset. Significant results (Table 5) were also obtained between the GFAP values at the onset of the 3rd day and impaired memory (p = 0.001), visuospatial (p = 0.016), language (p = 0.005), and executive (p = 0.005) at the onset of the 30th day.

Discussion

Among the 40 research subjects, the mean level (standard deviation) of serum GFAP was

Table 5: Domain test on cognitive impairment with GFAP levels

Disturbed domains	n (%)	GFAP		
		Average (sb)	Median (Min–Max)	p
Attention				
Onset day to 7	7 (38.89)	3.04 (1.86)	3.06 (0.77–5.17)	0.213*
Onset day to 30	3 (37.5)	3.22 (1.87)	3.06 (1.45–5.17)	0.257*
Improvement				0.565*
Language				
Onset day to 7	8 (44.4)	2.85 (1.92)	2.3 (1.21–6.18)	0.244*
Onset day to 30	4 (50)	4.68 (1.32)	4.74 (3.06–6.18)	0.005*
Improvement				0.449**
Memory				
Onset day to 7	12 (66.67)	3.0 (1.88)	3.06 (0.25–6.76)	0.162*
Onset day to 30	7 (87.5)	4.29 (1.89)	4.32 (1.45–6.76)	0.001*
Improvement				0.64*
Visuospatial				
Onset day to 7	6 (33.33)	4.25 (1.84)	4.38 (1.45–6.76)	0.004*
Onset day to 30	4 (50)	4.62 (2.25)	5.14 (1.45–6.76)	0.016*
Improvement				0.107**
Executive				
Onset day to 7	7 (38.89)	4.26 (1.68)	4.32 (1.45–6.76)	0.01*
Onset day to 30	5 (62.5)	4.56 (1.95)	5.1 (1.45–6.76)	0.005*
Improvement				0.107**

*Unpaired t-test, **Mann–Whitney test.

2.26 (1.53) μg/L. The lowest value was 0.25 μg/L and the highest value was 6.76 μg/L, with 1.93 μg/L as the median. This is consistent with the findings of Sarfo *et al*.), that GFAP concentrations have a stronger relationship to the incidence of ischemic stroke in lacunar and non-lacunar stroke compared to non-ischemic stroke [16].

Astroglial cells respond to ischemic stroke brain injury by undergoing reactive astrogliosis, a process in which astroglial cells undergo cellular hypertrophy (increase in size and expression of GFAP protein) and proliferation (increase in the number of glial cells). Ischemic stroke causes the release of GFAP-BDP, especially full-length GFAP from damaged astrocytes into the interstitial/extracellular fluid, where it equilibrates into the subarachnoid cerebrospinal fluid compartment before being released into the blood circulation through direct venous drainage (glymphatic pathway) or by diffusing across the blood-brain barrier (BBB). As a brain biomarker, one of the advantages of GFAP is having strong brain specificity and high expression in the brain [11], [17].

The 7th day's assessment with MoCA Ina revealed that the median score was 25.23 (2.37) and the range was between 17 and 30. The median value was 26. This demonstrates that ischemic stroke can impair cognitive function in addition to causing disability in the form of motor or sensory problems.

According to Mijajlović *et al*., amyloid deposition and inflammatory alterations in the brain after ischemia contribute to the development of cognitive impairment after stroke. Blood pressure lowering, statins, neuroprotective medications, anti-inflammatory drugs, lifestyle interventions, physical activity, and cognitive training have all been investigated as potential treatment strategies to slow the progression and shorten the course of the disorder, but no clear evidence of their efficacy has been found [18], [19].

In this study, MoCA Ina's score improved by 1.53 points on average. The majority of PSCI gets better after the subacute period (up to 3 months after stroke) or earlier. Cognitive impairment is present in between 50% and 90% of cases during the subacute phase. A determining factor for the development of cognitive function is the improvement of cerebral circulation caused by spontaneous recanalization, neuroplasticity, and the presence of concomitant problems at this phase. Most of the penumbra reperfused within 3 months of stroke. The size of the infarct and cognitive deficits tended to stabilize after 3 months. In this stage, cognitive improvement is also dependent on rehabilitation [9], [10], [20], [21], [22].

GFAP onset on the 3rd day had a significant relationship with the MoCA Ina score on the 7th day with p = 0.015, r = 0.381, and on the 30th day with p = 0.007, r = 0.418. GFAP onset on the 3rd day had a significant relationship with the MoCA Ina score on the 7th day with p = 0.015, r = 0.381, and on the 30th day with p = 0.007, r = 0.418. This is in accordance with Bettcher *et al*. research explaining that higher levels of GFAP than astrogliosis markers reflect poor memory function and white matter integration (white matter), regardless of amyloid or neurodegeneration markers. Astrocytes play a formative role in memory consolidation during physiological conditions. When dysregulated, the astrocytes release GFAP, which has been associated with negative memory outcomes [23].

According to a study by Shir *et al*., amyloid load and cognitive impairment may be related to plasma GFAP levels, but no association was found between plasma GFAP and specific cognitive domains (memory, attention, language, or visuospatial scores). Supporting this statement, Huang *et al*. studied 63 lacunar stroke patients, and 25 of them had cognitive impairments, where it was explained that reactive astrogliosis has a modulating effect on the development of PSCI. Patients with PSCI have an older age, lower education, and more severe cortical atrophy [24], [25], [26].

Verberk *et al*. stated that increased GFAP levels were associated with decreased levels in the MMSE and all other tests that measure memory, attention, and executive function. The accumulation of amyloid plaques also affects the decrease in attention and executive [27].

GFAP is a marker of brain damage when astrogliosis occurs. Astrocytes play an important role in supporting neuronal cells and maintaining synaptic function because the toe structures of astrocytes have contact with cerebral endothelial cells. The BBB maintains constant perfusion requirements consisting of neurovascular units composed primarily of astrocytes [28].

According to Asken *et al*., high levels of GFAP are associated with low executive and visuospatial function. Visuospatial and executive abilities involve large areas of the cerebral hemispheres. When ischemia occurs, the neurovascular structure is damaged due to astrogliosis, resulting in disruption of the integrity of the

white matter and damage to the BBB, which can cause neuronal damage, multisynaptic disturbances, and result in executive disorders. Plasma GFAP is sensitive to white matter and alters executive function both early in the disease and persistently in later stages of the disease [29].

From hippocampal biopsies, GFAP markers also correlate with the incidence of Alzheimer's dementia due to the accumulation of amyloid beta and impaired white matter integration in the temporal lobe. Therefore, GFAP is also important to memory function [23].

During the stroke recovery phase, astrocytes contribute to angiogenesis, neurogenesis, and synaptogenesis. Thus, faster recovery of astrocytes can improve neurological recovery and cognitive function. Therefore, greater markers of astrogliosis may decrease the recovery of cognitive function [30]. This is consistent with the study's findings that there was a significant relationship between GFAP levels and MoCA-Ina improvement. ($p = 0.031$, $r = -0.342$).

Levine *et al*. stated that, compared to younger survivors, older survivors experienced significantly faster declines in global cognition and executive function. However, the acute decline in global cognition and executive function after stroke did not differ by age. The effect of lacunar stroke on acute decline in executive function is modified by education level. Compared with stroke survivors who graduated from college, lacunar stroke survivors who had less than a high school education experienced a greater acute decline in executive functioning after stroke. The acute decline in global cognition after stroke is greater in men than in women [31]. According to Lo *et al* (2019), diabetes mellitus and a history of stroke are strongly associated with poorer cognitive function although there is no significant difference in affected domains between ethnic groups [32].

Statements from Danovska and Peychinska and the Sydney Stroke Study, showed that lesion volume is a significant determinant of post-stroke dementia, while pre-stroke cognitive function is a significant determinant of post-stroke cognitive decline during the first 3–6 months after a stroke attack. Frequently, massive infarction leads to dementia, but the clinical course is not progressive in most cases. The number of cerebral lesions has been found to be a significant determinant. Multiple infarctions often lead to progressive cognitive impairment and eventually to multi-infarct dementia. The previous multiple lesion strokes undoubtedly increase the risk of PSCI. It has been found that more severe clinical deficits at stroke onset are associated with a higher risk of post-stroke dementia. Particular attention is paid to "strategic infarction sites," which are cerebral infarctions that lead to dementia when cortical and subcortical areas that are important for cognition are damaged. The most frequent strategic sites were the left angular gyrus, mesial inferomesial and frontal temporal sites, thalamus, left internal capsule genu, and caudate nucleus [9].

Meanwhile, according to a study by Kartikasari *et al*., age, gender, hypertension, dyslipidemia, and the number and location of infarctions did not significantly affect the cognitive clinical outcome of patients with acute ischemic stroke. This is consistent with the findings of this study, there is not a single significant confounding variable for cognitive impairment. This may occur if study participants are well treated for confounding clinical variables before stroke [33].

Conclusion

There was a significant relationship between GFAP levels and the MoCA Ina score on the 7th and 30th days, and MoCA-Ina improved. Significant associations were found between GFAP levels and the executive, visuospatial, language, and memory domains. No significant relationship was found between GFAP levels and improvements in the attentional, memory, language, visuospatial, and executive domains.

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