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SERUM FERRITIN AS PROGNOSTIC MARKER IN ACUTE ISCHEMIC STROKE-AN OBSERVATIONAL STUDY

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ABSTRACT **Background:** Stroke is defined as "rapidly developing clinical evidence of focal (or global) impairment of brain function, with symptoms lasting 24 hours or more or leading to death, with no evident cause other than vascular origin," according to the World Health Organization. Many studies have suggested that serum ferritin may have a role in predicting iron-mediated free radical harm in the etiology of cerebrovascular disorders. A high serum ferritin level upon admission was linked to a poor prognosis in acute stroke patients (within 24-48 hours after start). The primary goal of this study is to evaluate the role of serum ferritin in patients with acute ischemic stroke.
Settings and Design: It is observational study carried out in 50 cases with ischemic stroke. Severity of stroke was determined using CSS score. Laboratory investigations were done to estimate serum ferritin.
Results: We found that the mean serum ferritin levels were significantly increased among "more severe stroke" and deteriorated stroke patients than compared to "less severe stroke" and not-deteriorated stroke patients (p<0.05). We found significant negative correlation with spearman's rho of -0.7 between serum ferritin and CSS score.
Conclusions: Serum ferritin plays a major role in predicting the severity and prognostic outcome of acute ischemic stroke.

KEYWORDS : Ischemic Stroke, Serum Ferritin, Canadian Stroke Scale.

INTRODUCTION

Cerebrovascular disease is the most debilitating neurological condition that affects humans. The term stroke, or apoplexy (Greek for "to be struck down"), refers to a sudden localized neurological condition, particularly one induced by cerebrovascular illness. Stroke is defined as "rapidly developing clinical evidence of focal (or global) impairment of brain function, with symptoms lasting 24 hours or more or leading to death, with no evident cause other than vascular origin," according to the World Health Organization.[1] Some of the early prognostic indications of ICH include radiological symptoms such as the size, location, and extent of the infarct, surrounding edema, Glasgow coma scale score (GCS), and intracranial tension.[2]

Strokes are prevalent, with a 42-100/10000 yearly incidence. Following heart failure, it is the second leading cause of death in Europe. After heart failure and cancer, it is the third leading cause of death in the United States. It is the world's second greatest cause of mortality in general.[3] India has a total of 6,398,000 DALYs[4]; 0.63 million deaths[5]; 1.44 million to 1.64 million new acute stroke episodes each year.[6] In India, the prevalence of stroke is 55.6 per 100,000 for all ages.[7]

Stroke has terrible consequences. Other vital mental skills like as humor, mood, initiative, and speed of reasoning are severely damaged, in addition to the functions unique to the destroyed brain tissue. Unfortunately, in the management of stroke victims, these characteristics often overlooked.

Iron has been found to play a key role in neurotoxicity and edema production following stroke in previous studies. Many studies have suggested that serum ferritin may have a role in predicting iron-mediated free radical harm in the etiology of cerebrovascular disorders. A high serum ferritin level upon admission was linked to a poor prognosis in acute stroke patients (within 24-48 hours after start). This elucidates the mechanism by which an increase in the body's iron reserves prior to the onset of a stroke aggravates the cytotoxicity of brain ischemia.[8,9] Only a few researches had previously reported on the significance of serum ferritin in the prognosis of acute ischemic stroke. As a result, this study was designed to correlate serum ferritin levels with early neurological status and to predict severity and prognosis in acute stroke patients earlier. The primary goal of this study is to evaluate the role of serum ferritin in patients with acute ischemic stroke.

MATERIALS AND METHODS

This was a hospital based observational study conducted in the department of General Medicine at HSK hospital, Bagalkot, Karnataka after obtaining institutional ethical committee approval. A group of 50 subjects participated in this study who had onset of symptoms of acute ischemic stroke within 48 hours which is diagnosed clinically and by computed tomography of brain. We have excluded those with anemia, severe alcohol consumption, chronic liver or kidney disease, hematological cancer and patients with recent infection or inflammation.

Pre-tested proforma designed for the study was used. On admission, a complete history was obtained from every patient including symptoms of headache, vomiting, loss of consciousness, seizures and focal neurological deficit. History of hypertension, diabetes mellitus, drug history including use of anticoagulation were noted. Clinical evaluation was carried out noting vital parameters, clinical signs of focal neurological deficit and signs of increased intracranial tension. Other systems were also examined to find significant comorbidities. Neurological assessment was done initially every day by Canadian stroke scale (CSS) from the day of admission and repeated on subsequent follow-up. The outcome of patients was classified into clinical improvement, deterioration, and death by the CSS. All patients were treated according to the established guidelines at the time of study. All the patients were subjected to non-enhanced computed tomography scan of the brain.

After getting informed consent from all the participants, 2ml of venous blood was collected by sterile venipuncture within 72 hours of symptom onset. Serum ferritin levels were estimated by ELISA method. Simultaneously renal function, liver function and complete blood count and peripheral smear study were carried out.

STATISTICAL ANALYSIS

The variables were analyzed using SPSS software version 22. Students t-test was employed to find out significance of difference between means in study patients. Chi-square test

was used to find an association between categorical variables. Variables are analyzed using one-way ANOVA between different prognostic groups. Spearman's correlation analysis was used to find correlation between serum ferritin and CSS. $p < 0.05$ was considered the threshold for statistical significance.

RESULTS
Demographics and risk factors
Among the total 50 cases included in final analysis, 64% were males and 36% were females with a mean age of 53.9 ± 11.9 years. Majority of stroke cases in our study were aged between 51-60 years (40%). On the basis of CSS score, the cases were divided into two groups namely "less severe stroke" group with CSS score >7 and "more severe stroke" group with CSS score ≤7. We found that there was no significant association between CSS and age, gender and co-morbidities. However, there was statistically significant association between mean serum ferritin levels and CSS score. The mean serum ferritin levels were much higher in "more severe stroke" compared to "less severe stroke" ($p < 0.05$). (Table 1)

Table 1: Characteristics of stroke patients in our study based on CSS scores.

Variables		Less severe stroke (CSS score >7)	More severe stroke (CSS score ≤7)	p-value
Mean Age in years		54.11±13.05	52.7±11.06	0.684
Mean serum Ferritin (ng/ml)		200.93±44.1	312.4±63.5	<0.001
Age groups	<40 years	3 (15%)	8 (26.7%)	0.473
	41 to 50 years	5 (25%)	3 (10%)	
	51 to 60 years	7 (35%)	13 (43.3%)	
	61 to 70 years	4 (20%)	3 (10%)	
	>71 years	1 (5%)	3 (10%)	
Gender	Male	12 (60%)	20 (66.7%)	0.765
	Female	8 (40%)	10 (33.3%)	
Risk factors	Hypertension	9 (45%)	16 (53.3%)	0.564
	Diabetes Mellitus	9 (45%)	15 (50%)	0.729

The mean CSS score was 7.15 ± 2.12 in the study population. The mean serum ferritin was 253.8 ± 79.1 ng/ml in the study population. Table 2 shows the comparison of mean serum ferritin levels and mean CSS score in various baseline demographic and co-morbidities group. It is evident that neither serum ferritin nor mean CSS score varied with respect to age, gender and co-morbidities ($p > 0.05$)

Table 2: Comparison of serum ferritin level and CSS score among study participants

Variables		Serum Ferritin (Mean ±SD)	CSS (Mean±SD)
Age groups	<40 years	238.6±59.2	7.23±1.8
	41 to 50 years	285±43.7	6±2.15
	51 to 60 years	251.3±77.7	7.65±2.2
	61 to 70 years	256.4±134.6	7.21±2.04
	>71 years	221.3±48	8.38±2.4
p-value		0.672	0.338
Gender	Male	242.03±71.4	7.25±2.1
	Female	270.3±86.2	7.36±2.2
p-value		0.219	0.861
Hypertension	Present	245±91.2	7.78±2.1
	Absent	259.4±61.7	6.8±2.1
p-value		0.516	0.103
Diabetes Mellitus	Present	251.04±90.7	7.31±1.9
	Absent	253.3±65.7	7.27±2.4
p-value		0.92	0.943

Table 3 shows the comparison of various parameters with

outcome of ischemic stroke in our study. The outcome of patients was described as either deteriorated or not-deteriorated. We found that the mean serum ferritin levels were significantly increased among deteriorated stroke patients than compared to not-deteriorated stroke patients ($p < 0.05$). Figure 1 shows the correlation between serum ferritin and CSS score. We found significant negative correlation with spearman's rho of -0.7 between serum ferritin and CSS score.

Table 3: Comparison of various parameters with outcome of stroke

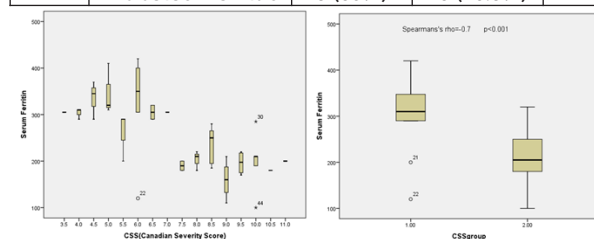| Variables		Outcome		p-value
		Deteriorated	Not-deteriorated	
Mean Age in years		51.8±14.3	54.4±10.7	0.481
Mean serum Ferritin (ng/ml)		285±72.1	233.8±75.1	**0.023**
Gender	Male	13 (72.2%)	19 (59.4%)	0.54
	Female	5 (27.8%)	13 (40.6%)	
Risk factors	Hypertension	6 (33.3%)	19 (59.4%)	0.14
	Diabetes Mellitus	9 (50%)	15 (46.9%)	1

Figure 1: Correlation between serum ferritin and CSS score among stroke patient

DISCUSSION
The interruption of blood flow due to extracranial or cerebral thrombosis, embolism, or hypoperfusion causes an ischemic stroke. Previous research has revealed that iron overload promotes thrombosis following arterial injury, which may contribute to the development of vascular disease. Furthermore, a high serum ferritin level upon admission has been linked to a poor prognosis in acute stroke patients, suggesting that an increase in body iron reserves prior to the beginning of the stroke can exacerbate the cytotoxicity of brain ischemia. As a result, it's been proposed that a high serum ferritin level influences the prognosis of ischemic stroke and also works as a risk factor for ischemic episodes by promoting atherogenesis.[10,11]

Our research involved 50 individuals who had an acute ischemic stroke and were admitted within 48 hours after the onset of symptoms. When compared to "less severe stroke" and non-deteriorated patients, mean serum ferritin levels in "more severe stroke" and deteriorated stroke patients were significantly higher. Pankaj P et.al.[12], Narayan and Singh[13], E Govindarajulu et al.[14], Erdemoglu AK et.al.[15], and Koul et al.[16] all observed comparable findings. A statistically significant negative connection was discovered between serum ferritin levels and CSS scores in this investigation. Many theories have been offered to explain this connection. Serum ferritin levels that are higher suggest that the body has more iron stores.

This is reflected in the brain's iron reserves as well. Because the wounded brain cells have bigger iron reserves, more iron will be released when brain ischemia occurs during CVA. When more iron is released, the local environment of the wounded tissue experiences more oxidative stress as a result of the production of free radicals, particularly hydroxyl radicals. As a result, tissue injury during ischemia is aggravated. Furthermore, because of reperfusion injury, which produces even more iron release and increased

oxidative stress, this tissue insult is amplified after reperfusion.[12] Another theory is that when brain cells with higher iron reserves are harmed during ischemia, they release more glutamate, which then causes more tissue injury.[12] As a result, serum ferritin appears to be linked to the severity of the condition.

Study Limitations:
1. Single center study with small sample size.
2. Serum ferritin levels at the time of discharge and follow-up would better predict the prognosis of ischemic stroke.

CONCLUSION:
The present study reveals a significant correlation of serum ferritin with the severity of acute ischemic stroke, depicting elevated admission serum ferritin levels has no good prognosis.

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