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Original Research Article

Serum ferritin as a prognostic marker in acute stroke; a cross-sectional observational study

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ABSTRACT

Background: Stroke is the leading cause of morbidity and mortality all over the world. Several prognostic factors like site and size of infarction, Glasgow coma scale, level of cerebral edema, intracranial tension have been found significant in stroke. Among the prognostic indicators ferritin has gained importance in recent times. It is considered an acute phase reactant and has been used for assessing the severity and prognosis of stroke. Aim of the study was to correlate the levels of serum ferritin with early neurological status and to predict the severity and prognosis earlier in patients of acute stroke.
Methods: This cross-sectional observational study was done in Saveetha hospital, Chennai. Clinically diagnosed CVA patients within 48 hours of the onset of symptoms were recruited in this study. 122 patients above 18 years who fulfilled the criteria were included and patients with a recent history of inflammation, malignancy, and anemia were excluded.
Results: Around 60.7% of patients had improved and the remaining of them deteriorated. The level of serum ferritin was well correlated with the patient's prognosis. Those who deteriorated had high serum ferritin when compared to those who improved and it was statistically significant.
Conclusions: From our results, we concluded that patients with increased ferritin concentrations have a higher risk of poor clinical outcomes. These findings suggest that iron overload may counterbalance the benefits of thrombolytic therapy in patients with high ferritin levels. Therefore, serum ferritin can be used as a prognostic marker for assessing the severity and prognosis of stroke.

Keywords: Stroke, Ferritin, Prognostic marker

INTRODUCTION

Stroke or cerebrovascular accident (CVA) is defined as an abrupt-onset neurological deficit attributable to a focal vascular cause.[1] It is the second leading cause of death and the third leading cause of disability.[2] As per WHO, stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin".[3] Radiological signs such as size, site, and extent of the infarct, surrounding edema, Glasgow coma scale score (GCS), and intracranial tension are some of the early prognostic indicators of ICH.[4] Past research has already shown that iron plays a very important role in neurotoxicity and edema formation after stroke. The possible role of serum ferritin in predicting iron-mediated free radical injury in the pathogenesis of cerebrovascular diseases is portrayed in many studies. According to Van der et al elevated serum ferritin levels were associated with higher risks of ischemic stroke.[5] Previous studies have suggested that iron overload contributes to development of vascular disease by promoting thrombosis after arterial injury. Poor prognosis in acute stroke patients (within 24-48 h after stroke onset) was well correlated with high serum ferritin at admission. This reveals the possible mechanism that an increase in the body's iron stores before

stroke onset aggravate cytotoxicity of brain ischemia.[6,7] Earlier very few studies only reported role of serum ferritin in the prognostication of acute ischemic stroke. Therefore, intended to do this study to correlate the levels of serum ferritin with early neurological status and to predict severity and prognosis earlier in patients of acute stroke.

METHODS

This cross-sectional observational study was conducted at Saveetha medical college and hospital, Chennai. This study was done between January 2018-October 2019.122 patients above 18 years who fulfilled the criteria were included and the patients with a recent history of inflammation, malignancy, and anemia were excluded.

A diagnosis of stroke was made clinically and its Pathophysiology was confirmed by CT scan. Repeat CT was taken when necessary. Serum ferritin was performed on admission within 48 hours of the onset of symptoms, by electrochemiluminescence immunoassay. 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.

Statistical analyses were performed by using a statistical software package SPSS, version 20.0. A Chi-square test was used to find an association between categorical variables. Normally distributed continuous variable's mean was assessed by student's t-test. For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance.

CSS

CSS is a simple and validated score to assess the stroke severity. Lower scores indicate greater stroke severity. It includes the following components: Level of consciousness, orientation, speech, and motor functions. Stroke severity is categorized as follows. Mild (greater or equal to 8), moderate (score 5 to 7), severe (score 1 to 4). The score range is 1.5 to 11.5

RESULTS

Categorical and quantitative variables were expressed as frequency (percentage) and mean ± SD respectively. A Chi-square test was used to find an association between categorical variables. Normally distributed continuous variable's mean was assessed by Student's t-test. For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance.

Table 1 illustrates the background characteristics of our subjects. Among the 122 subjects in our study, 71% had an ischaemic stroke and the rest of them had a hemorrhagic stroke. Males occupied a greater number in our study which was around 67%. All the individuals with hemorrhagic stroke had hypertension as a predisposing factor and only 9% of them had dyslipidemia. About 65% of subjects with ischemic stroke were improved and in hemorrhagic stroke, only 51% of them were improved, remaining of them deteriorated.

Table 1: Comparison of background characteristics between ischemic and hemorrhagic stroke patients by using chi-square test.

Factors		Percentage distribution of stroke patients		χ^2	P value
		Ischemic stroke, (n=87) (%)	Hemorrhagic stroke, (n=35) (%)		
Age (Year)	30-50	23 (26.4)	11 (31.4)	0.321	0.855 (ns)
	51-70	51 (58.6)	19 (54.3)		
	71-90	13 (14.9)	05 (14.3)		
Sex	Male	58 (66.7)	24 (68.6)	0.041	0.839 (ns)
	Female	29 (33.7)	11 (62.9)		
Smoking	Yes	45 (51.7)	22 (37.1)	1.249	0.264 (ns)
	No	42 (48.3)	13 (25)		
Alcoholic	Yes	39 (44.8)	16 (45.1)	0.008	0.929 (ns)
	No	48 (55.2)	19 (54.3)		
Hypertension	Yes	61 (70.1)	35 (100)	13.293	0.000***
	No	26 (29.9)	0 (0.0)		
Diabetes mellitus	Yes	67 (77)	16 (45.7)	11.241	0.001***
	No	20 (23)	19 (54.3)		
Dyslipidemia	Yes	26 (29.9)	03 (8.6)	6.257	0.017**
	No	61 (70.1)	32 (91.4)		
CSS	Improved	56 (64.4)	18 (51.4)	1.751	0.132 (ns)
	Deteriorated	31 (35.6)	17 (48.6)		

***p<0.01-*p<0.05 (alpha value)-statistically significant, ns-not significant.

Table 2: Comparison of CSS between ischemic and haemorrhagic stroke patients by using chi-square test.

Percentage distribution of stroke patients	CSS, n (%)		Total, n (%)	χ^2	P value
	Improved	Deteriorated			
Ischemic stroke	56 (64.4)	31 (35.6)	87 (100)	1.751	0.132 (ns)
Haemorrhagic stroke	18 (51.4)	17 (48.6)	35 (100)		
Total	74 (61)	48 (39)	122 (100)		

Table 3: Comparison of serum ferritin level and CSS among the stroke patients by using student 't' test.

Stroke	Serum ferritin level, n (%)		T value	P value
	Improved, mean ± SD	Deteriorated, mean ± SD		
Ischemic stroke	144.48±134.65, (56)	362.45±153.41, (31)	-6.878	0.001***
Haemorrhagic stroke	139.14±151.21, (18)	369.36±193.80, (17)	-3.931	0.001***
Total	143.18±137.8, (74)	364.9±166.7, (48)	-7.667	0.000***

Values are expressed in mean ± SD; SD-Standard deviation; *p<0.05- **p<0.01- statistically significant, ns- not significant.

Table 2 compares the CSS between ischaemic and hemorrhagic stroke patients. The 64.4% and 51.4% of the ischaemic stroke and hemorrhagic stroke subjects were improved respectively and the remaining of them deteriorated. Overall, around 61% of the subjects improved.

Comparison of serum ferritin level and CSS among the stroke patients is depicted in Table 3. The level of serum ferritin was comparatively very much lower in the subjects who were improved and it was found to be highly statistically significant (p=0.000).

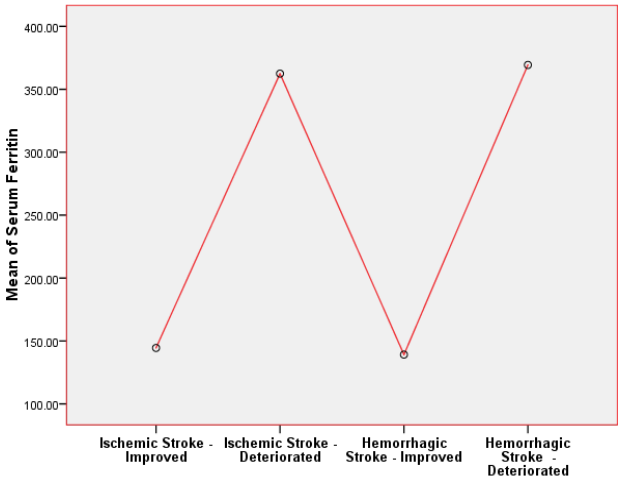

Figure 1: Comparison of serum ferritin level and CSS among the stroke patients.

DISCUSSION

Our study is one of the earliest studies to find the correlation between serum ferritin levels with the prognosis of stroke in the South Indian region. Serum ferritin is a suitable index of the amount of cellular iron stored in the body. It is also related to the availability of iron in the affected area of the brain.[8,9] In the brain, the non-haem iron is stored in microglia and astrocytes as ferritin.[10] During hypoxia and oxidative stress, the synthesis of ferritin is increased in the brain in response to the accumulation of reactive oxygen species. This happens as a part of neuroprotection, to quench reactive oxygen species.[11,12] Ferritin catalyzes the conversion of superoxide and hydrogen peroxide into highly reactive hydroxyl radical, during a state of cerebral hypoperfusion.[13]

In our study, we have reported that the serum ferritin levels were higher in the subjects whose condition deteriorated and it is found to be highly statistically significant. The mean value of ferritin in the deteriorated patients was 364.9±166.7 and that of the improved patients was 143.18±137.8. Mehdiratta et al reported a positive correlation between the serum ferritin levels and the perihematomal edema in patients of spontaneous cerebral hematoma.[14] In the earlier research, it was established that serum ferritin was considered to be an independent predictor of long-term functional outcomes in neuro critically ill patients.[15]

There are many predictive theories behind the correlation between serum ferritin and the prognosis of stroke patients. Higher serum ferritin levels indicate higher body stores of iron. This is also applicable to the iron stores in the brain. When there is brain ischemia during CVA, more iron will be released from the injured brain cells due to larger iron stores present in them. This, in turn, causes the generation of more free radicals due to an increasing in oxidative stress in the injured tissue. Eventually, there is an aggravation of tissue injury during ischemia.[1] The molecular basis for the brain damage secondary to iron overload is due to the generation of radical hydroxyl from oxygen during reperfusion, increased excitotoxicity, and blood-brain barrier disruption.[16]

Ferritin, being an acute-phase protein, should be estimated within 72 hours of symptom onset to eliminate any possible elevations in an acute phase reaction. We have analyzed the serum ferritin levels within 48 hours of admission and found a positive correlation between serum ferritin and the worse prognosis. Interestingly, iron chelation was found to reduce infarct size, brain edema, and metabolic failure in ischemia.[17] Therefore, in future

studies, iron chelators or free radical trapping agents can be used to reduce the neurotoxic effects of iron in patients with acute ischemic stroke.

The limitation of the study is that it is a single centre study and the sample size could have been increased to know the exact significance of the study. Long term follow up of the stroke patients need to be done to assess the exact severity and prognosis.

CONCLUSION

We have found that the patients with stroke with increased serum ferritin concentrations have a higher risk of poor clinical outcomes than patients with low ferritin values. Elevated serum ferritin level not only predicts early neurological deterioration but also helps in decision-making regarding thrombolytic therapy. Thus, serum ferritin can act as a prognostic marker in acute stroke.

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REFERENCES

1. Pankaj P, Das M, Sing MK. Association between level of serum ferritin and outcome of patients of stroke. J Evol Med Dent. 2015;4:2023-36.
2. Global Health Estimates. Geneva: World Health Organization; 2012. Available at: http://www.who.int/healthinfo/global_burden_disease/en. Accessed on 10 February 2020.
3. The world health organization MONICA project (monitoring trends and determinants in cardiovascular disease): A major international collaboration. WHO MONICA project principal investigators. J Clin Epidemiol. 1988;41:105-14.
4. Rådberg JA, Olsson JE, Rådberg CT. Prognostic parameters in spontaneous intracerebral hematomas with special reference to anticoagulant treatment. Stroke. 1991;22(5):571-6.
5. Van der A DL, Grobbee DE, Roest M, Marx JJ, Voorbij HA, Van der Schouw YT. Serum ferritin is a risk factor for stroke in post-menopausal women. Stroke. 2005;36(8):1637-41.
6. Njajou OT, Hollander M, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM et al. Mutations in the hemochromatosis gene (HFE) and stroke. Stroke. 2002;33:2363-6.
7. Millán M, Sobrino T, Arenillas JF, Rodríguez-Yáñez M, García M, Nombela F et al. Biological signatures of brain damage associated with high serum ferritin levels in patients with acute ischemic stroke and thrombolytic treatment. Dis Markers. 2008;25:181-8.
8. Walters GO, Miller FM, Worwood M. Serum ferritin concentration and iron stores in normal subjects. J Clin Pathol. 1973;26:770-2.
9. Connor JR, Menzies SL, St Martin SM, Mufson EJ. Cellular distribution of transferrin, ferritin, and iron in normal and aged human brains. J Neurosci Res. 1990;27:595-611.
10. Walters GO, Miller FM, Worwood M. Serum ferritin concentration and iron stores in normal subjects. J Clin Pathol. 1973;26:770-2.
11. Connor JR, Menzies SL, St Martin SM, Mufson EJ. Cellular distribution of transferrin, ferritin, and iron in normal and aged human brains. J Neurosci Res. 1990;27:595-611
12. Orino K, Lehman L, Tsuji Y, Ayaki H, Torti SV, Torti FM et al. Ferritin and the response to oxidative stress. Biochem J. 2001;357:241-7.
13. Selim MH, Ratan RR. The role of iron neurotoxicity in ischemic stroke. Ageing Res Rev. 2004;3:345-53.
14. Castellanos M, Puig N, Carbonell T, Castillo J, Martinez J, Rama R et al. Iron intake increases infarct volume after permanent middle cerebral artery occlusion in rats. Brain Res. 2002;952:1-6.
15. Mehdiratta M, Kumar S, Hackney D, Schlaug G, Selim M. Association between serum ferritin level and perihematomaedema volume in patients with spontaneous intracerebral hemorrhage. Stroke. 2008;39:1165-70.
16. Xie L, Peng Y, Huang K, Wu Y, Wang S. Predictive value of iron parameters in neurocritically ill patients. Brain Behav. 2018;8(12):e01163.
17. Selim MH, Ratan RR. The role of iron neurotoxicity in ischemic stroke. Ageing Res Rev. 2004;3:345-53.
18. Davis S, Helfaer MA, Traystman RJ, Hurn PD. Parallel antioxidant and antiexcitotoxic therapy improves outcome after incomplete global cerebral ischemia in dogs. Stroke. 1997;28:198-204.

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