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Original Article

Role of Serum Ferritin in Determining the Severity and Prognosis of Stroke: A Hospital Based Study

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Abstract

Introduction: Stroke is one of the major causes of morbidity and mortality the world over. Various scores have been applied to assess the severity and prognosis of stroke. Serum ferritin which is considered as an acute phase reactant has also been used for assessing the severity and prognosis of stroke.

Purpose: The purpose of this study was to access the applicability of serum ferritin as a surrogate marker of stroke severity and prognosis.

Materials and Methods: A study was conducted in the Department of Medicine in Government Medical College, Srinagar, where 50 patients with stroke were enrolled for the study and their modified Rankin scale (MRS) and National Institute of Health Stroke Scale (NIHSS) were calculated, and a statistical correlation was found with the level of serum ferritin.

Results and Conclusion: A statistically significant correlation was found between NIHSS and MRS scores and serum ferritin levels in acute stroke patients, thus paving the way for further research on the topic.

Key words: Modified Rankin scale, National Institute of Health Stroke Scale, Serum ferritin, Stroke

INTRODUCTION

According to the WHO, stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer or leading to death, with no apparent cause other than of vascular origin"[1] according to this definition if the symptoms last for <4 h, it is excluded from the definition of stroke and is known as transient ischemic attack, it also excludes by definition stroke syndromes caused due to subdural hemorrhage, tumors, poisoning, or trauma.

Stroke is among the leading cause of deaths in India,[2] as on the basis of verbal autopsy in a population of 180,162 living in 45 villages in Andhra Pradesh, it was found that stroke is responsible for deaths in 13% of population just 1% less than coronary artery disease which leads with 14%. The 30-day case fatality as reported in Kolkata was 41.08%.[3] According to the Indian Council of Medical Research, stroke and diabetes combined caused a national economic loss of approximately 46 billion dollars in India between 2006 and 2015.[4]

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Although there has been a tremendous progress made in the field of stroke, still the exact prognostication of stroke is not possible. Several indicators such as the size of, in fact, the vessel involved, the presenting Glasgow coma scale (GCS), the amount of edema surrounding the infarct, and the intracranial pressure have been used as an index to access the severity and to prognosticate acute ischemic stroke. Similarly, in the case of hemorrhagic stroke, the volume of the hemorrhage as calculated on the CT scan, the GCS, and the location of the bleed has been used widely for the purpose.

Research has shown that iron plays a very important role in neurotoxicity and edema formation after stroke.

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Hemoglobin degradation after erythrolysis releases iron, and it is also released from ferritin stores and is highly neurotoxic by catalyzing hydroxyl radical formation and promoting oxidative stress.[5] Ferritin has widely been used in medicine as a body indicator of iron stores. It, however, also, is an acute phase reactant which is responsible for defending the cell against the free radical-mediated oxidative stress and edema.[6]

MATERIALS AND METHODS

The study was an observational cross-sectional (prospective) study carried out at Government Medical College from August 2016 to February 2017. Patients were selected randomly who were admitted in the Medicine Department of the hospital for the said period.

Inclusion Criteria

- All patients who presented as acute-onset focal neurodeficit who presented within 48 h of the symptoms were included in the study.
- Patients with new onset of stroke with previous comorbidities such as hypertension, dyslipidemia, diabetes, smoking, and alcohol were included in the study.
- All the subjects included were more than 18 years of age.

Exclusion Criteria

- Patients more than 80 years were excluded from the study.
- Those having clinical, laboratory, or radiological evidence of central nervous system (CNS) infection were excluded from the study.
- Patients with recent history of trauma and surgery were excluded from the study.
- Patients with CNS malignancies and other structural brain deformities were also excluded from the study.

As soon as patient got admitted, verbal consent was obtained from patient or attenders. Then, complete relevant medical history, neurological examination, routine blood, and CT scan were done, and all data were recorded in a standardized pro forma.

Quantitative estimation of serum ferritin was done among the included patients within 48 h of presentation using the electrochemiluminescence immunoassay "ECLIA" in Elecsys and cobas immunoassay analyzer.

We used two scores (a) National Institute of Health Stroke Scale (NIHSS) score and (b) modified Rankin score (MRS) to evaluate the severity of the stroke in the patients that fulfilled the inclusion criteria of our study.

The National Institutes of Health Stroke scale or NIHSS is a scale which is used by health-care providers and researchers to objectively estimate the impairment caused by a stroke. The NIHSS is made up of 11 parameters, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment.[7] The individual scores from each item are summed to calculate a patient's total NIHSS. The maximum possible score is 42, with the minimum score being a 0 [Table 1].[8,9]

The MRS is another scale that is used for measuring the degree of disability or dependence in the day-to-day activities of people who have suffered a stroke. It is one of the most commonly used tools to measure the clinical outcome in stroke clinical trials.[10,11]

The scale runs from 0 to 6, running from perfect health without symptoms to death.

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, and incontinent.
- 6 - Dead.

All the collected data were computed in master chart. Statistical data analysis was done. Chi-Square test, mean, standard deviation, and *P* values were calculated. $P < 0.05$ denotes statistically significant relationship.

Pearson's R correlation test and scatter plot analysis were also done for given data.

RESULTS

Our study included 50 patients of stroke that was admitted in medicine department of our hospital. Serum ferritin value of these patients was obtained in all the patients and the NIHSS and MRS were calculated in all of them.

A maximum value of serum ferritin was found to be 467 ng/ml, the lowest value was 47 ng/ml, and the mean value was 278.2 ng/ml [Table 2].

The minimum, maximum, and the mean value of the NIHSS were 2, 19, and 12.24, respectively, and that of MRS were 1, 6, and 3.02, respectively [Table 2].

Statistical analysis revealed that there was a significant correlation between the values of serum ferritin and NIHSS ($P < 0.001$) and the MRS ($P < 0.001$).

After applying the Pearson's R correlation and the scatter plot analysis, it was found that serum ferritin and NIHSS and MRS have a very strong correlation and that any increase or decrease in the serum ferritin had a directly proportional change in the values of NIHSS [Table 3 and Figure 1] and MRS values [Table 3 and Figure 2].

DISCUSSION

Our study which is the first of its kind from the Kashmir region shows that there is a significant correlation between the values of serum ferritin and the other well-validated stroke prognosis and severity scores, that is, NIHSS and MRS. These observations were true in case of both ischemic and hemorrhagic strokes. Admission serum ferritin levels were very high in patients having a high NIHSS and MRS value.

Serum ferritin is a representative of the level of iron stores in the cells of the body and consequently might be related to the level of iron present in the affected area of the brain.[12,13] Most of the non-Heme iron in brain is in the form of ferritin and is stored in the astrocytes and the microglia.[14] Hypoxic acidosis and oxidative stress may induce the brain increase the level of ferritin[15] to reduce the accumulation of reactive oxygen species.[16] Thereby, it may act as a neuroprotector in such cases.

Free iron that is released from the cerebral stores, for example, ferritin catalyzes the conversion of superoxide and hydrogen peroxide into highly reactive hydroxyl radical, during a state of cerebral hypoperfusion.[17,18] Increased iron intake has been associated with larger in fact volumes, more oxidative stress, glutamate release, and inflammatory response after middle cerebral artery occlusion in rat models.[19] On the other hand, iron chelation was found to reduce infarct size, brain edema, and metabolic failure in ischemia/reperfusion stroke model.[20,21]

Worse neurological outcome, high blood glutamate levels, and larger infarct volume were seen in patients who have not received thrombolytic therapy and had high serum

Table 1: NIHSS

Score	Stroke severity
0	No stroke symptoms
1–4	Minor stroke
5–15	Moderate stroke
16–20	Moderate to severe stroke
21–42	Severe stroke

NIHSS: National Institute of Health Stroke Scale score

Table 2: Descriptive statistics

Variable	*N*	Mean±SD	Min.	Max.
Serum ferritin	50	278.2±141.9	47	467
NIHSS score	50	12.24±4.52	2	19
MRS	50	3.02±1.84	1	6

MRS: Modified Rankin score, NIHSS: National Institute of Health Stroke Scale score, SD: Standard deviation

Table 3: Karl Pearson's correlation of serum ferritin with NIHSS score and modified Rankin score

Variable	*n*	Pearson correlation	*P* value
Serum ferritin - NIHSS score	50	0.904	<0.001*
Serum ferritin - MRS	50	−0.836	<0.001*

*Statistically significant correlation at 0.05 level, MRS: Modified Rankin score, NIHSS: National Institute of Health Stroke Scale score

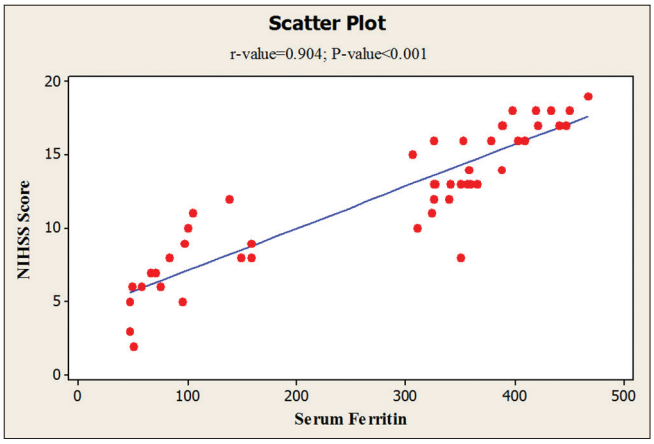

Figure 1: The association between the National Institute of Health Stroke score and serum ferritin

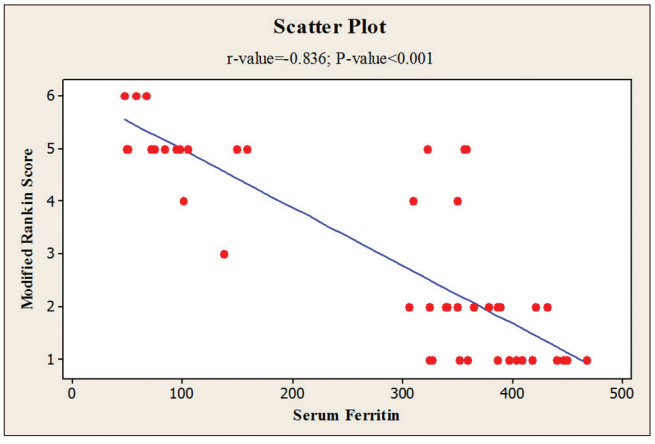

Figure 2: The association between modified Rankin score and the serum ferritin

ferritin levels and high cerebrospinal fluid levels of ferritin.[22,23]

A positive correlation was found between the serum ferritin levels and the perihematoma edema in patients of spontaneous cerebral hematoma.[24]

In summary, patients suffering from stroke and those having increased serum ferritin concentrations have a poor clinical outcome, have associated more brain edema, and have a higher risk of hemorrhagic transformation than those patients who have a low serum ferritin value. If further studies conducted on this topic confirm the results of our study, it can make a place for iron chelation therapy in the management of stroke patients, both hemorrhagic and ischemic and especially the ones who are treated with reperfusion therapy as they have a high risk of free radical-mediated brain damage occurrence.

CONCLUSION

Our study which is an observational cross-sectional (prospective) study that was conducted in acute stroke patients indicated that high values of serum ferritin were associated with high NIHSS, which indicated the severity of the stroke also it had a positive correlation with the MRS which indicates poor outcome in high MRS patients of acute stroke. Further, research on the topic can help us to use serum ferritin as a surrogate marker for stroke severity and can help us to prognosticate the patients of stroke and can further pave the way for the use of iron chelation in therapy of stroke patients and can, thus, help us to take a big leap forward in the management of stroke patients.

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