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PROGNOSIS OF PATIENTS IN ACUTE ISCHEMIC STROKE AND ITS ASSOCIATION WITH SERUM FERRITIN: A PROSPECTIVE COHORT STUDY

Medicine

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ABSTRACT

Despite lot of researches in the field of stroke, accurate prognostication of an acute attack is difficult. Several prognostic factors like site of infarction, size of infarct etc., have been found significant in cerebral infarction. One of the prognostic indicators which has gained great clinical interest in recent times is the level of serum ferritin. Initially considered only as a stress response to stroke, serum ferritin is now under research as a prognostic indicator, with increased concentrations having a higher risk of poor clinical outcomes.

KEYWORDS

INTRODUCTION

A Stroke or Cerebrovascular Accident (CVA) is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" by WHO.[1] An ischemic stroke is further defined as "an episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction.[2] Thus the definition of stroke is clinical, and laboratory studies including brain imaging are required to support the diagnosis.[3]

Cerebrovascular disease is the third leading cause of death after heart diseases and cancer in developed countries and is now emerging as the commonest preventable life threatening neurological problem worldwide. Improved detection and modification of risk factors could reduce the impact of this disease. Important non-modifiable risk factors include age, gender, ethnicity and heredity. Modifiable risk factors include hypertension, cardiovascular disease, diabetes, hyperlipidemia, asymptomatic carotid stenosis, cigarette smoking and alcohol abuse.[3]

Several factors like site of infarction, size of infarct, size of the vessel involved, Glasgow coma scale, level of cerebral edema, intracranial tension have been found to be significant in prognosis of cerebral infarction. Some upcoming prognostic indicators under study include hyperglycemia in stroke, infection in stroke, TNFα/ interleukins etc. Initially considered only as a stress response to stroke, serum ferritin has gained great clinical interest in recent times, and is now under research as an important prognostic indicator, the possible mechanisms of which are discussed under. This has also enhanced research in the therapeutic role of iron chelation in improving stroke prognosis. In most hospitals, not much can be done for stroke patients other than conservative management. Proving the therapeutic potential of iron chelation therapy will be a great advancement in the field of treatment of stroke.[4,5,6,7]

MATERIAL AND METHODS

A total of 23 patients having stroke and presenting within 48hrs of onset of symptom(s) were included in the study after diagnosis was confirmed by CT scan. Neurological assessment was done by Canadian Stroke Scale (CSS). Serum ferritin was assessed within 48 hours of onset of symptoms. Neurological assessment was repeated on 6th day of admission by CSS again. Patients were classified into those with clinical improvement, deterioration and death. In vitro quantitative determination of ferritin in human serum was done by electro chemiluminescence immunoassay "ECLIA" in Elecsys and Cobas e immunoassay analyzer.

Study Design: Prospective cohort study

Study Location: Department of General Medicine, Rajendra Institute of Medical Sciences, Ranchi

Study Duration: October 2016 to September 2017.

Sample size: 23 patients.

Inclusion criteria:

1. Patient should be aged above 18 years.
2. Both sexes are included.
3. Diagnosis of CVA should be confirmed by CT scan.
4. Patient should present within 48 hours of onset of symptoms.

Exclusion criteria:

1. Patient not fulfilling inclusion criteria.
2. Patients with history of recent infection or inflammation in the previous month.
3. Patient with history of malignancy.
4. Patients with anaemia.

Statistical analysis

Pair wise comparison between various variable was done for different parameters. The Range, Mean value, Standard Deviation (S.D.), Standard error of Mean, 't' value and 'p' values were calculated as per the applicability by using appropriate formulas. Statistical Package of Social Sciences (SPSS) v. 22 was used for the purpose of data entry and data analysis. Chi-square test was used to find out associations (relations) between 2 categorical variables, ANOVA test was used to find out associations between multiple categorical variables. Pearson's correlation coefficient was used for numerical variables and p-value less than 0.05 was regarded as statistically significant.

CANADIAN STROKE SCALE

Date Time			
Mentation	Level of Consciousness	Alert	3
		Drowsy	1.5
	Orientation	Oriented	1
		Disoriented/Inapplicable	0
	Speech	Normal	1
		Expressive Aphasia	0.5
		Receptive Aphasia	0

No Comprehensive Deficit Section A1	Motor Function		Weakness
	Face	None	0.5
		Present	0
	Arms: Proximal	None	1.5
		Mild	1
		Significant	0.5
		Total	0
	Arms: Distal	None	1.5
		Mild	1
		Significant	0.5
		Total	0
	Legs: Proximal	None	1.5
		Mild	1
		Significant	0.5
		Total	0
	Legs: Distal	None	1.5
		Mild	1
		Significant	0.5
		Total	0
Comprehensive Deficit Section A2	Face	Symmetrical	0.5
		Asymmetrical	0
	Arms	Equal	1.5
		Unequal	0
	Legs	Equal	1.5
		Unequal	0
Total			

Result

Total sample size: 23
Males: 14
Females: 9
Age range: 26-85
Followings were the findings of the present study-

Table No 1: Distribution of outcomes

Outcome	n	Percentage
Number of cases improved	16	69.6
Number of cases deteriorated	7	30.4
Total	23	100

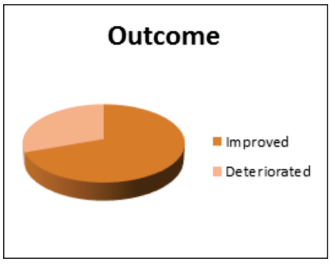

Table No 2: Sex distribution of patients with ischemic stroke

	n	Percentage
Male	14	60.86
Female	9	39.14

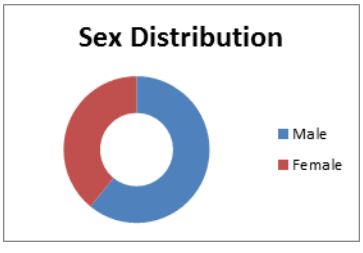

Table No 3: Age distribution of patients with ischemic stroke

Age range	n
20-30	1
31-40	1
41-50	6
51-60	7
61-70	5
71-80	2
81-90	1

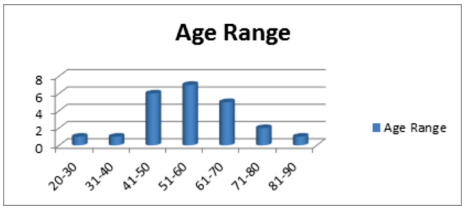

Table No 4: Mean serum ferritin of patients with ischemic stroke

	Mean Serum Ferritin
Patients which improved	87.01
Patients which deteriorated	458.70

Table No 5: Descriptive statistics of serum ferritin in patients with ischemic stroke who improved

Mean	87.013125
Median	52.44
Standard Deviation	73.53128284
Range	238.2
Minimum	20.2
Maximum	258.4

Table No 6: Descriptive statistics of serum ferritin in patients with ischemic stroke who deteriorated

Mean	458.7014286
Median	416.16
Standard Deviation	145.4344779
Range	385
Minimum	321
Maximum	706

Table No 7: t-test assuming unequal variances to compare means of serum ferritin of improved and deteriorated groups in ischemic stroke

	Improved	Deteriorated
Mean	87.01313	458.701429
Observations	16	7
Df	7	
t Stat	6.41268	
P(T<=t) two tail	0.000363	
t Critical two tail	2.364624	

INFERENCE:

There is statistically significant difference in means of the two groups with $p<0.001$.

Mean serum ferritin in deteriorated patients is significantly higher than those who improved.

DISCUSSION

This study shows that serum ferritin is an important independent risk factor of prognosis of stroke. High levels of serum ferritin correlate well with the early neurological deterioration of stroke patients. Therefore testing of serum ferritin can be helpful in identifying high risk patients. Other risk factors are evenly distributed among both the groups. But the mean serum ferritin in the improved group was significantly lower than the group which deteriorated. Admission levels of serum ferritin were found to be significantly higher in patients who deteriorated in next 7 days. Serum ferritin is a suitable index of the amount of cellular iron stores and, consequently, might be related to the availability of iron in the infarcted area.[8,9] In brain tissue, most of the non-heme iron is in the form of ferritin, which is localized in astrocytes and microglia.[10] Ferritin synthesis in brain cells may be induced in hypoxic acidosis or in response to oxidative stress to reduce the accumulation of reactive oxygen species.[11] Therefore, increased ferritin could be in part the result of a neuro-protective mechanism with the aim of sequestering non-toxic iron in the ischemic brain.

During cerebral ischemia, free iron released from intracellular stores such as ferritin catalyzes the conversion of superoxide and hydrogen peroxide into the highly reactive and toxic hydroxyl radical.[12,13] Experimental data support a causal role of iron overload in ischemic brain and endothelial damage. Iron intake has been associated with larger infarct volumes, higher oxidative stress, glutamate release, and inflammatory response after permanent middle cerebral artery occlusion in rats,[14] whereas iron depletion or chelation reduces infarct size, brain edema, and metabolic failure in ischemia/reperfusion

experimental stroke models.[15,16] In patients with acute ischemic stroke not treated with thrombolytic drugs, high serum ferritin values and high cerebrospinal fluid ferritin concentrations determined early after symptom onset have been associated with subsequent neurologic worsening, poor neurologic outcome, large infarct volume, and elevated concentrations of glutamate in blood.[17,18]

As it has specific areas rich in iron, high amounts of polyunsaturated fatty acid side chains in membrane lipids, and low concentrations of antioxidant enzymes, the brain may be especially vulnerable to oxidative stress. So far, only a few articles have reported on the association between iron and the risk of stroke in population-based studies. Taken together, these findings suggest that iron overload is associated with following-

a. Poor early neurological outcome in stroke patients.

b. Iron overload may offset the beneficial effect of thrombolytic therapy.

c. Iron chelation therapy may be beneficial in acute stroke if serum ferritin is high.

Studies done previously in this field have shown similar results. In summary, patients with stroke and increased serum ferritin concentrations have a higher risk of poor clinical outcome, hemorrhagic transformation, and brain edema than patients with low ferritin values. These findings suggest that iron overload may counterbalance the benefits of thrombolytic therapy observed in patients with low ferritin levels. If these results are confirmed in future studies, iron chelators or free radical trapping agents should be used to reduce the neurotoxic effects of iron in patients with acute ischemic stroke and those who are treated with thrombolytic therapy.

CONCLUSION

A number of evidence has suggested that elevated serum ferritin is a definite prognostic marker of acute ischemic stroke. An elevated serum ferritin heralds more intensive management protocols and care for the patient as it can predict early neurological deterioration. It can help in decision making regarding thrombolytic therapy. Patients can be classified as those who will be benefited or not from the thrombolytic therapy. Those with elevated serum ferritin will have more chances of deterioration in post-thrombolysis period. Iron chelation therapy can actually improve the prognosis of stroke. Many studies are on to prove actual therapeutic efficacy of iron chelation therapy (Desferrioxamine and defepirome) in acute stroke. But this study at least shows its theoretical possibility. Strict thrombolysis protocols, late presentation of patients after the crucial period of first three hours when thrombolysis can be performed and delay in radiological diagnosis due to lack of facilities does not leave much for the clinician to do in these cases except for conservative management. Iron chelation therapy, if proved to be beneficial in future can take us a big leap forward in the management of acute stroke.

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