To establish the role of serum ferritin as a prognostic marker in patients of stroke

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Abstract

Introduction: Stroke is the second leading cause of death worldwide. The incidence of cerebrovascular diseases increases with age. 1 Accurate prognostication of stroke patients is difficult many times.

Materials and Methods: A total of 100 stroke patients who presented to R.N.T. Medical College Udaipur Rajasthan were enrolled from February 2016 to October 2016 and their serum ferritin was measured and correlated with early neurological deterioration in patients of acute stroke.

Results: Total 100 patients were included, the age ranged from 22-90 years and the age group with the maximum number of patients was 61-70 years. 62 patients were in ischemic and 38 were in hemmoraghic groups. In ischemic group the mean serum ferritin level was 89.540 in clinically improvement patients and 341.345 in those deteriorated. In hemorrhagic group the mean serum ferritin level was 86.838 in clinically improvement patients and 355.759 in those deteriorated.

Conclusion: The patients with stroke with increased serum ferritin concentrations have a higher risk of poor clinical outcome, hemorrhagic transformation, and brain edema than patients with low ferritin values.

Keywords: Serum ferritin, Ischemic stroke, Hemorrhagic transformation.

Introduction

Stroke is a major cause of disability worldwide. The incidence of cerebrovascular diseases increases with age, and the number of strokes is projected to increases as the elderly population grows.[1,2] Despite a lot of researches in the field of stroke, accurate prognostication of an acute attack is very difficult. Several prognostic factors like site and size of infarct, size of the vessels involved, Glasgow coma scale (GCS), level of cerebral edema, intracranial tension have been found significantly in cerebral infarction. Similarly, in cases of cerebral hemorrhage, CT calculated volume of hematoma, GCS, site of hemorrhage etc. are important. Some of the upcoming prognostic indicators are under study e.g.; hyperglycemia in stroke, infections in stroke, TNF alpha or interleukins etc.

One of the prognostic indicators which have gained great clinical interest in recent times is the level of serum ferritin. Initially it was considered only a stress response to stroke, serum ferritin now is under research as a prognostic indicator. This has also enhanced research in the therapeutic role of iron chelation in improving stroke prognosis. Proving serum ferritin as a prognostic marker and in turn therapeutic potential of iron chelation therapy will be a great advancement in the management of stroke.[3-5]

Aims and Objectives

1. To study the effect of concentration of serum ferritin on the outcome of patients of acute stroke.
2. To correlate the levels of serum ferritin with early neurological deterioration in patients of acute stroke.
3. To correlate the levels of serum ferritin in patients with early neurological deterioration to hemorrhagic transformation in acute ischemic stroke and increase in perihematomal edema volume in spontaneous intracerebral hemorrhage.

Materials and Methods

Study Area: The study was conducted in R.N.T. Medical College and Associated Groups of Hospitals, Udaipur in southern Rajasthan. The main catchment area is rural with few township and municipal area.

Study Population: All the patient admitted in the department of General Medicine and Neurology with history suggestive of stroke.

Study Period: All the patients included in the study was selected within a specified period from February 2016 to October 2016

Sample Size: A total number of 100 patients diagnosed as cases of stroke was taken during this time period for this study.

Inclusion Criteria:

1. Patient should be aged above 18 years.
2. Both sexes are included.
3. Diagnosis of stroke should be confirmed by CT scan/MRI Brain.
4. Patient should present within 48 hrs. 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 anemia

Methods of Collection of Data

1. Data was collected from a total of 100 patients of cerebrovascular disease (proven radiologically) presenting within 48 hours of onset symptoms, irrespective of their age, gender, religion or socioeconomic status.
2. Diagnosis of stroke was confirmed with the help of an CT/MRI scan of brain.
3. Detailed history and examination of patient was enquired and entered in Performa. In addition, neurological assessment was done by Canadian stroke scale.
4. Serum Ferritin was estimated within 48 hours of onset of symptoms along with Complete Blood Count (CBC), Random Blood Sugar (RBS), C-Reactive Protein (CRP), blood urea, creatinine, liver function test.
5. Neurological assessment was repeated on the 5th day of admission or before if condition of the patient deteriorates with Canadian stroke scale.
6. Repeat CT/MRI was done if condition of the patient deteriorated.

Plan for Data Analysis: At the end of the study, the data was compiled, tabulated and analyzed for variation of means and correlation by appropriate biomedical software. The SPSS for the windows ver. 16.00 statistical package program was used in the evaluation of the data. Appropriate test of significance was applied i.e. Chi-square test for qualitative data and Student's' test was applied for quantitative data. p value less than 0.05 was considered significant.

Canadian Neurological Scale (CNS):[18-21] The Canadian Neurological Scale (CNS) was developed as a simple tool to be used in the evaluation and monitoring of neurological status of patients with stroke in the acute phase (Cote, Hachinski, Shurvell, Norris & Wolfson, 1986). The CNS evaluates 10 clinical domains, including mentation (level of consciousness, orientation and speech) and motor function (face, arm and leg).

The CNS is comprised of 8-items measuring the level of consciousness, orientation, speech, motor function and facial weakness.[20,21]

1. If patient is alert or drowsy: monitor with CNS (sections A1 and A2)
2. If patient is stuporous or comatose: monitor with Glasgow coma scale

Mentation

Level of Consciousness

1. Alert 3.0
   Spontaneous eye opening, normal level of consciousness
2. Drowsy 1.5
   When stimulated verbally patient remains awake and alert but tends to doze

Orientation

1. Oriented 1.0
   Where are you? (City and Hospital)
   What is the month and year?
   Speech can be slurred but must be intelligible.
2. Disoriented 0.0
   Patient cannot state both place and time or cannot express answers in words or intelligible speech.
   It is acceptable for patient to write answer to questions of orientation

Speech

1. Receptive deficit 0.0
   Ask pt. 1) to close eyes; 2) Point to ceiling; 3) Does a stone sink in water?
   If pt. does not complete the above 3, go to Section A2.
2. Expressive deficit 0.5
3. Normal Speech 1.0

Scoring and Score Interpretation

1. Mentation: Comprised of evaluating consciousness, orientation and speech.
2. Motor function evaluations are separated into sections A1 and A2. A1 is administered if the patient is able to understand and follow instructions. A2 is administered in the presence of comprehension deficits.[20] Each motor item is rated for severity and each rating is weighted "according to the relative importance of a particular neurological deficit".[21]
3. It should be noted that assessment using the CNS focuses on limb weakness over other possible neurological impairments.[21]
4. The CNS scores only the motor strength of the weakest limb. For patients with a comprehension deficit, asymmetry in strength is scored. Therefore, in addition to using the CNS, clinicians may wish to further evaluate and document the upper and lower extremity strength and power in patients with comprehensive deficit.
5. Scores from each section are summed to provide a total score out of a possible 11.5. Lower scores are representative of increasing severity.

Results

Ischemic Stroke: The sex distribution in the 62 cases of ischemic stroke was, 37 cases (59.67%) being males and 25 cases (40.32) females. The age ranged from 22-90 years and the age group with the maximum number of patients was 61-70 years.

Table 1: Sex distribution of patients of ischemic stroke

	Number	Percent
Males	37	59.67
Females	25	40.32

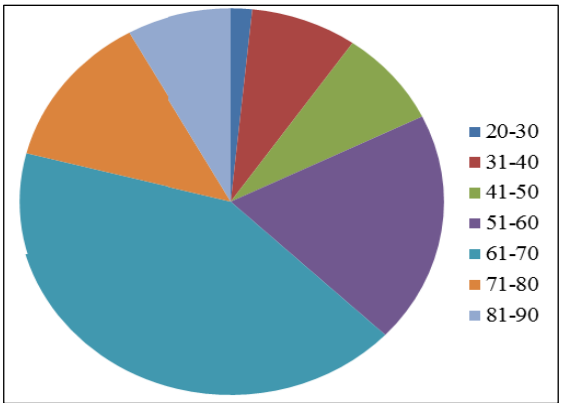

Fig. 1: Graphical representation of age distribution of Ischemic stroke cases

The number of cases that showed improvement on the 5th day of assessment was 40, while 22 cases deteriorated. The sex distribution in the clinically improved group was 23(57.5%) males and 17 (42.5%) females and in the deteriorated group were 14(63.6%) males and 8(36.3%) females. The mean age of the patients that showed improvement was 63.40 years and the mean age of the patients deteriorated was 62.95 years. There was statistically insignificant difference between the mean age and gender distribution of the improved and deteriorated group (p values being 0.907 and 0.637 respectively).

The mean serum ferritin level of the group of patients that showed clinical improvement was 89.540 and those deteriorated was 341.345.

Out of the 22 cases of deterioration 16 cases had associated hemorrhagic transformation of infarct while 6 cases did not. This correlation was found to be statistically significant (p<0.001).

The descriptive statistics of serum ferritin of patients of ischemic stroke who improved and deteriorated was derived that is the mean, median, standard deviation, range, minimum and maximum. Then t-test assuming unequal variances to compare means of serum ferritin of improved and deteriorated groups in ischemic stroke was applied.

Table 2: Descriptive statistics of serum ferritin of patients of ischemic stroke who improved

Mean	77.165
Median	53.550
Standard deviation	58.1679
Range	170
Minimum	9.8
Maximum	179.8

Table 3: Descriptive statistics of serum ferritin of patients of ischemic stroke who deteriorated

Mean	341.345
Median	324.500
Standard deviation	99.8947
Range	572
Minimum	158.3
Maximum	730.3

Table 4: T –Test assuming unequal variances to compare means of sreum ferritn of improved and deteriorated groups in ischemic stroke

	Improved	Deteriorated
Mean	89.540	341.345
Observations	40	22
Df	60	
T Stat	-9.833	
P(T<=t) two tail	0.0003	

The inference being:

*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

Hemorrhagic Stroke: The sex distribution in the 38 cases of Hemorrhagic stroke was, 24 cases (63.15%) being males and 14 cases (36.84) females. The age ranged from 41-90 years and the age group with the maximum number of patients was 71-80 years. The number of cases that showed improvement on the 5th day of assessment was 16, while 22 cases deteriorated. The sex distribution in the clinically improved group was 11(68.75%) males and 5 (3.125) females and in the deteriorated group was 13(59.09%) males and 9 (40.09%) females. The mean age of the patients that showed improvement was 65.69 years and the mean age of the patients deteriorated was 66 years. There was statistically insignificant difference between the mean age and gender distribution of the improved and deteriorated group (p values being 0.942 and 0.735 respectively)

Table 5: Mean serum ferritin of patients of hemorrhagic stroke

	Mean Serum Ferritin
Patients improved	86.838
Patients deteriorated	355.759

The mean serum ferritin level of the group of patients that showed clinical improvement was 86.838 and those deteriorated was 355.759.

Table 6: Distribution of day-5 CT/MRI changes (perilesional oedema) in deteriorated hemorrhagic stroke patients

	D5-CT/MRI changes (present)	D5-CT/MRI Changes (absent)
Hemorrhagic Stroke (Deteriorated)	18	4

Out of the 22 cases of deterioration 18 cases had associated edema formation after ICH while 4 cases did not. This correlation was found to be statistically significant ($p<0.001$)

The descriptive statistics of serum ferritin of patients of hemorrhagic stroke who improved and deteriorated was derived that is the mean, median, standard deviation, range, minimum and maximum. Then t-test assuming unequal variances to compare means of serum ferritin of improved and deteriorated groups in hemorrhagic stroke was applied.

Table 7: Descriptive statistics of serum ferritin of patients of hemorrhagic stroke who improved

Mean	86.838
Median	68.550
Standard deviation	88.2059
Range	363.8
Minimum	22.7
Maximum	386.5

Table 8: Descriptive statistics of serum ferritin of patients of hemorrhagic stroke who deteriorated

Mean	355.759
Median	359
Standard deviation	31.8665
Range	100
Minimum	296
Maximum	396

Table 9: T–test assuming unequal variances to compare means of sreum ferritn of improved and deteriorated groups in hemorrhagic stroke group

	Improved	**Deteriorated**
Mean	86.838	355.759
Observations	16	22
df	36	
tStat	-13.218	
P(T<=t) two tail	0.00002	

The inference being:

*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 in the hemorrhagic group

Discussion

The above study showed 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.[8-11] Therefore, testing of serum ferritin can be helpful in identifying high risk patients. As seen in the observations, the mean age of the patients in the improved and deteriorated groups is almost the same. 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. This holds true in both ischemic and hemorrhagic stroke.[12-15] Admission levels of serum ferritin were found to be significantly higher in patients who deteriorated in next 5 days. This study also suggests that a high serum ferritin level is an important predictor of hemorrhagic transformation in patients with acute ischemic stroke and the levels correlate with edema formation after ICH.[7,16,17,23]

These findings suggest that iron overload is associated with following;

1. Poor early neurological outcome in stroke patients.
2. Iron overload may be associated with hemorrhagic transformation in acute ischemic stroke and edema formation after ICH.[6,22] Many studies are on to prove actual therapeutic efficacy of iron chelation therapy (Deferoxamine and defepirome) in acute stroke.[24] But this study at least shows its theoretical possibility. The 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.[7] The Iron chelation therapy, if proved to be beneficial in future can take us a big leap forward in the management of acute stroke.

The patients with stroke with increased serum ferritin concentrations have a higher risk of poor clinical outcome, hemorrhagic transformation, and brain edema than patients with low ferritin values.[6,16,17] 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.

References

1. Harrison's Principles of Internal Medicine 19th Edition, page 2559.
2. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global burden of disease study. *Lancet* 1997;349:1269-76.
3. Emile Millerot-Serrurot, Nathalie Bertrand, Claude Mossiat, Philippe Faure, Anne priget-Tessier, *Neurochemistry International* 2008 June 8;52(8)1442-1448.
4. Herbert V, Jayatilleke E, Shaws, Rosman A S, Giardina P, Grady R W, Bowman B, Gunter E W, Serum Ferritin Iron, a new test, measures human body iron stores unconfounded by inflammation. Stem cells;1997;291-296.
5. Walters G O, Miller F M, Worwood M.Serum ferritin concentrations & iron strores in normal subjects *J Clin Pathal*. 1973;26:770-772.
6. Mehdiratta M at al, Stroke. 2008 Apr;39(4):1165-70 doi:10.1161/Strokeaha.107.501213.

7. White BC, Grossman LI, O'Neil BJ, DeGracia DJ, Neumar RW, Rafols JA, Krause GS (1996) Global brain ischemia and reperfusion. *Ann Emerg Med* 27:588–594.
8. Zecca L, Youdim MB, Riederer P, Connor JR, Crichton RR (2004) Iron, brain ageing and neurodegenerative disorders. *Nat Rev Neurosci* 5:863–873.
9. Selim MH, Ratan RR (2004) the role of iron neurotoxicity in ischemic stroke. *Ageing Res Rev* 3:345–353.
10. Carbonell T, Rama R (2007) Iron, oxidative stress and early neurological deterioration in ischemic stroke. *Curr Med Chem* 14:857–874.
11. Lou M, Lieb K, Selim M (2009) the relationship between hematoma iron content and perihematoma edema: An MRI study. *Cerebrovasc Dis* 27:266–271.
12. Galaris D, Skiada V, Barbouti A (2008) Redox signaling and cancer: the role of "labile" iron Cancer Lett 266:21–29.
13. Kurz T, Terman A, Gustafsson B, Brunk UT (2008) Lysosomes in iron metabolism, ageing and apoptosis. *Histochem Cell Biol* 129:389–406.
14. Perez de la Ossa N, Sobrino T, Silva Y, Blanco M, Millan M, Gomis M, Agulla J, Araya P, Reverte S, Serena J, Davalos A (2010) Iron-related brain damage in patients with intracerebral hemorrhage. Stroke 41:810–813.
15. Millan M, Sobrino T, Castellanos M, Nombela F, Arenillas JF, Riva E, Cristobo I, Garcia MM, Vivancos J, Serena J, Moro MA, Castillo J, Davalos A (2007) Increased body iron stores are associated with poor outcome after thrombolytic treatment in acute stroke. Stroke 38:90–95.
16. Reif DW. Ferritin as a source of iron for oxidative damage. Free Radic Biol Med. 1992;12:417–427.
17. Castellanos M, Puig N, Carbonell T, Castillo J, Martı´nez JM, Rama R, Da´valos A. Iron intake increases infarct volume after permanent middle cerebral artery occlusion in rats. *Brain Res*. 2002;952:1–6.
17. Cote, R., Hachinski, V., Shurvell, B., Norris, J. & Wolfson, C. (1986). The Canadian Neurological Scale: A preliminary study in acute stroke. *Stroke*, 17(4), 731-737.
18. Muir, K.W., Weir, C.J., Murray, G.D., Povey, C., Lees, K.R. (1996). Comparison of neurological scales and scoring systems for acute stroke prognosis. *Stroke*, 27, 1817-1820.
19. Nilanont, Y., Komoitri, C., Saposnik, G., Cote, R., Di Legge, S., Jin, Y. et al. (2010). The Canadian Neurological Scale and the NIHSS: Development and validation of a simple conversion model. *Cerebrovascular Disease*, 30(2), 120-126.
20. Cote, R., Battista, R.N., Wolfson, C., Boucher, J., Adam, J., Hachinski, V. (1989). The Canadian Neurological Scale: Validation and reliability assessment. Neurology, 39, 638-643.
21. Davalos A, Fernandez-Real JM, Ricart W, Soler S, Molins A, Planas E, Genis D. Iron-related brain damage in acute ischemic stroke. Stroke. 1994;25:1543–1546.
22. Choi KH, Park MS, Kim JT, Nam TS, Choi SM, Kim BC, et al. The serum ferritin level is an important predictor of hemorrhagic transformation in acute ischemic stroke. Eur J Neurol 2012 Apr; 19(4):570-7.
23. Gu Y, Hua Y, Keep RF, Morgenstern LB, Xi G (2009) Deferoxamine reduces intracerebral hematoma-induced iron accumulation and neuronal death in piglets. Stroke 40:2241–2243.