

## Is the serum ferritin level a considerable predictor for hemorrhagic transformation of ischemic stroke?

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### Abstract

**Background:** Hemorrhagic Transformation (HT) of Ischemic Stroke (IS) is a detrimental complication. This study investigated the association between serum ferritin level and HT in patients with massive IS of middle cerebral artery.

**Methods:** Thirty patients with massive IS of middle cerebral artery were enrolled in this prospective cohort study. They were divided into two groups based on the serum ferritin level, lower or greater than 164.1ng/ml at the first 24 hours after admission. To investigate the incidence of HT in the two groups, we observed them for two weeks.

**Results:** During the two-week observation, the incidence of HT was two persons (13.3%) in the group with the serum ferritin level of lower than 164.1ng/ml, and eight persons (53.3%) in the other group. This difference was statistically significant between the two groups ( $p=0.02$ ). The relative risk of HT was 4 (95% CI: 1.012-15.8) in the patients with massive IS of middle cerebral artery and the serum ferritin level greater than 164.1ng/ml.

**Conclusion:** This study revealed that the serum ferritin level greater than 164.1ng/ml in the first 24 hours after admission is a reasonably important predictor for HT of IS. Conducting studies on factors affecting the serum ferritin level are suggested.

**Keywords:** Stroke, Hemorrhagic Transformation, Ferritin.

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### Introduction

Hemorrhagic Transformation (HT) of Ischemic Stroke (IS) is a relatively frequent complication occurring in 2.2% to 44% of clinical cases (1). HT is related to poor prognosis of patients with IS. Additionally, it is one of the main obstacles for on time initiation of thrombolytic therapy (2). Some known risk factors for HT suggested by previous studies are severity of IS, old age, history of diabetes mellitus, the time to reperfusion, thrombolytic therapy, use of Aspirin and other anticoagulant drugs (1,3,4). Recent studies revealed that the serum ferritin level could be a novel predictor for HT (5,6).

Experimental studies supported the effect of iron overload in the ischemic brain and

endothelium damage. Iron intake was associated with the larger size of infarction, higher oxidative stress and more inflammatory response in IS model of rats (7). Iron depletion or chelation decreases the size of infarction, brain edema and neurological deficits in the cerebral ischemic-reperfusion experimental models (8,9).

A few clinical evidences exist in favor of this issue. In patients with IS, who were not treated by thrombolytic therapy, the high serum level and cerebrospinal fluid (CSF) level of ferritin were associated with poor neurological outcome and larger size of infarction (10-12). In another study on patients with IS, it was found that high serum ferritin level can be an important predicting factor for HT. This study suggested that the

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serum ferritin level of greater than 164.1ng/ml could be an independent predicting factor for HT with 85% sensitivity and 75% specificity (6). Furthermore, in a research on the IS patients treated by intravenous recombinant tissue plasminogen activator (rtpa), high serum ferritin level was concluded as a predictor for symptomatic HT and severe brain edema (5).

Considering the important role of HT in mortality and morbidity of IS patients (6) and lack of sufficient clinical researches to evaluate serum ferritin level as a predictor of HT, this cohort study was conducted to examine the association between serum ferritin level and HT of IS.

## Methods

### *Participants*

This prospective cohort study was conducted on patients with acute massive ischemic stroke (IS) of middle cerebral artery admitted within 24 hours after their symptoms onset at the Stroke Unit of Firoozgar general hospital in Tehran during April 2012 and February 2014. The patients with acute massive IS of middle cerebral artery were included in this research. Acute massive IS was defined as acute obstruction of the stem of middle cerebral artery which results in ischemia of more than 30% of the middle cerebral artery territory. They were divided into two groups based on serum ferritin level greater or lower than 164.1ng/ml. This cut off has been suggested in previous studies (6). Patients with the following conditions were excluded from the study: Patients with a history of conditions that may have influenced the serum ferritin level including liver disease, chronic inflammatory conditions (Rheumatoid arthritis, inflammatory bowel disease and bacterial infections), malignancy, thyrotoxicosis and alcohol consumption more than 40g/day; cases expired in the first 24 hours of admission; and patients under treatment for diseases related to iron. Finally, 30 patients were enrolled. The Medical Ethics Committee of Iran University of Medical Sciences and Firoozgar Clinical Research

Development Center (FCRDC) approved this study. All cases who participated in the study provided informed consent. In case of patients with low level of consciousness, the next-of-kin was asked to sign the consent form. All investigations were consistent with the declaration of Helsinki.

### *Assessments*

Demographic characteristics and baseline data of the patients including age, sex, history of medical conditions (stroke, diabetes mellitus and hypertension), history of smoking, history of alcohol consumption, drug history of anti-platelet therapy and primary clinical signs at admission (systolic blood pressure, diastolic blood pressure and body temperature) were collected from the medical records in check lists filled by neurology residents in the emergency unit and in the Stroke Unit of Firoozgar general hospital. Within 24 hours of admission, the patients' blood samples were sent to the laboratory to examine the serum ferritin level and prothrombin time and platelet count. All patients were diagnosed with brain computed tomography (CT) scan at the time of admission and followed for HT by repeating brain CT scan on the first and fifth days of admission, and each time a significant change was observed in the clinical condition of the patients during the two-week follow up. All brain CT scans were interpreted by one radiologist for diagnosing HT, which was defined as any hyper density changes in the stroke area. To evaluate the etiology of stroke, echocardiography and transcranial color doppler were done. All patients were treated based on the American Stroke Association guideline (15) for acute IS.

### *Statistical Analysis*

Data were analyzed using SPSS software 21. Prevalence rate and mean as central indices and standard deviation (SD) as an index of dispersion were used to describe the qualitative and quantitative variables. The statistical differences between the two proportions were assessed by Pearson chi

square test. Additionally, independent t-test was used to compare the two means. All tests' hypotheses were two-tailed, and the probability-value of less than 0.05 was considered statistically significant.

## Results

Thirty patients with massive IS of middle cerebral artery admitted in the stroke unit of Firoozgar general hospital were enrolled. They were divided into two groups: 15 cases in the group with serum ferritin level of greater than 164.1ng/ml (group A), and 15 with serum ferritin level of lower than 164.1ng/ml (group B). The mean (SD) age of the participants was 66.0 (17.5). Fifteen patients (50%) were male and 15 (50%) were female. The baseline characteristics of each group are displayed in Tables 1 and 2.

According to this table, the comparison of all baseline characteristics between the two groups was not statistically significant ( $p > 0.05$ ).

After the two-week follow up, HT was observed in eight cases (53.3%) of group A and in two cases (13.3%) of group B. The

difference between the incidence rates of HT was statistically significant in the two groups ( $p = 0.020$ ). The relative risk (RR) of HT was 4 (95% CI: 1.012-15.8) in the patients with massive IS of middle cerebral artery and serum ferritin level upper than 164.1ng/ml.

## Discussion

This study vigorously supported a few previous clinical studies, which had shown the association between serum ferritin level and hemorrhagic transformation (HT) of ischemic stroke (IS). The prospective cohort nature of this study makes its results more reliable.

A significant difference was found between the incidence rates of HT in the two groups, which were separated, based on the serum ferritin level greater or lower than 164.1ng/ml. The relative risk of HT of IS was estimated 4 (95% CI 1.012-15.8) in the patients with serum ferritin level of greater than 164.4ng/ml in this study.

The experimental studies revealed the role of increased iron in the stress oxidative

Table 1. Qualitative Baseline and Laboratory Characteristics of the Cases

Probable confounders	Category	Group A*	Group B**	p
Gender	Male	6 (40%)	9 (60%)	0.270
	Female	9 (60%)	6 (40%)	
History of hypertension	-	10 (66.7%)	7 (46.7%)	0.260
History of diabetes mellitus	-	5 (33.3%)	3 (20%)	0.680
History of Stroke	-	2 (13.3%)	2 (13.3%)	0.999
History of anti-platelet therapy	-	7 (46.7%)	4 (26.7%)	0.250
History of Smoking	-	3 (20%)	3 (20%)	0.999
History of Alcohol consumption	-	3 (20%)	2 (13.3%)	0.620
Stroke etiology	Cardioembolic	6 (40%)	7 (46.7%)	0.710
	Thrombotic	9 (60%)	8 (53.3%)	
Thrombolytic Therapy	-	1 (6.7%)	3 (20%)	0.590

\*N (%): The Group with Serum Ferritin Level > 164.1

\*\* N (%): The Group with Serum Ferritin Level < 164.1

Table 2. The Descriptive Statistics of Baseline and Laboratory Characteristics of the Cases

Probable confounders	Group A*	Group B**	p
Age	69.67 ( $\pm 10$ )	62.04 ( $\pm 22.04$ )	0.260
Systolic blood pressure at admission	145.4 ( $\pm 31.8$ )	151.33 ( $\pm 29.7$ )	0.600
Diastolic blood pressure at admission	85.53 ( $\pm 16.29$ )	88.2 ( $\pm 15.02$ )	0.640
Body Temperature at admission	36.72 ( $\pm 0.47$ )	36.49 ( $\pm 0.5$ )	0.200
Platelet count	218.27 ( $\pm 86.53$ )	204.93 ( $\pm 63.48$ )	0.630
Protrombin Time	13.85 ( $\pm 1.7$ )	12.93 ( $\pm 0.56$ )	0.064

\* Mean and ( $\pm$ SD): The Group with Serum Ferritin Level > 164.1

\*\* Mean and ( $\pm$ SD): The Group with Serum Ferritin Level < 164.1

reactions, inflammatory responses and vascular endothelium damage in the ischemic brain (7-9). Castellanos M et al. demonstrated that the increase in the iron intake was associated with the increase of extent of infarction after obstructing the middle cerebral artery of rats (7). In the studies on the experimental cerebral ischemic-reperfusion models of the dogs and gerbils by Davis S et al. and Patt A et al. in separate studies, it was concluded that the group treated by iron chelator drug had lower complications of brain ischemia (8-9). The results of our study were clinically compatible with those of the mentioned experimental studies.

A small number of clinical assessments were found in the literature review, probing the relationship between serum ferritin level as an indicator of tissue iron store (13,14), and one of the most important complications of IS: HT. Some clinical studies illustrated that the high serum ferritin level in the patients with IS at the first 24 hours of admission was related to the severity of stroke, increase of size of the lesion and poor prognosis (10-12). However, the effect of serum ferritin level on HT was not determined in these studies. Kerényi L et al. and Lindley RI found some risk factors of HT including old age, history of diabetes mellitus, the extent of infarction, drug history of anti-platelet medications and thrombolytic therapy (3,4). We included the patients with massive IS of middle cerebral artery and evaluated all the risk factors at the baseline data gathered from the patients. Choi KH et al. in a study on 752 patients with IS addition to introducing serum ferritin level as an important predicting factor of HT, suggested 164.1ng/ml as a cut off for serum ferritin level (OR=4.993) (6). The outcome of our study was consistent with this suggestion. Notably, considering the retrospective analytical nature of that study, the results of our prospective cohort research were more confirmatory. Moreover, in another investigation by Millan M et al., increased body iron stores were associated with poor out-

come after the thrombolytic treatment in acute IS (5). In this study, four patients were treated with thrombolytic therapy, though their frequencies were not significantly different between the two groups.

Small sample size and short time of the follow up were weak points of this study. Furthermore, because ferritin is an acute phase reactant, so many confounding conditions influence its serum level (6). Hence, impossibility of eliminating all factors affecting serum ferritin level in spite of our maximum efforts, limits the interpretations of our findings. Conducting multi-centric studies with long-term follow-ups and larger sample sizes is highly recommended.

### Conclusion

Our study confirmed the findings of previous studies, which found that serum ferritin level was a predicting factor for HT of IS. Consequently, the serum ferritin level of greater than 164.1ng/ml in the first 24 hours after admission of the patients with acute IS can be considered as a red flag to gain more attention when managing these patients, particularly during anticoagulant and thrombolytic therapy. The effect of interventions on reducing the serum ferritin level, such as phlebotomy and iron chelator medications, can be the subject of additional studies in the future.

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