Assessment of serum ferritin and thyroid hormones level in acute ischemic stroke and their association with hemorrhagic conversion

Richa Giri, Faim Ahamed*, Saurabh Agarwal, Lalit Kumar

Department of Medicine, KPS Institute, GSVM Medical College, Kapur, Uttar Pradesh, India

Received: 01 March 2021
Accepted: 03 April 2021

*Correspondence:
Dr. Faim Ahamed,
E-mail: faim786ahmad@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Acute ischemic stroke is a significant cause of mortality and the leading cause of long-term disability in the United States. Collective evidence suggests that low T3 levels and serum ferritin levels instantly following acute ischemic stroke are connected with greater stroke sterness, higher death rates, and poor functional outcomes. The aim of the study was to assess the serum ferritin and thyroid hormones level in acute ischemic stroke their association with hemorrhagic conversion.

Methods: In this observational study, 60 acute ischemic stroke patients aged ≥ 18 years of both gender who were reported with focal neurological deficit lasting greater than 24 hours were included. Clinical severity of stroke was assessed at admission and on the 7th day using Glasgow coma scale (G.C.S.), serum ferritin level, and thyroid hormones level were measured at admission and on the 7th day in all these subjects.

Results: Overall mean age of patients was 56.28±11.45 years with a range of 29-87 years; 61.7% were male patients. Ischemic stroke was found in 55 (91.7%) patients, while 5 (8.3%) patients showed hemorrhagic conversion. Serum Ferritin and T3 level shows a significant association with G.C.S. score (p<0.05). Hemorrhagic Conversion patients were significantly greater in-hospital stay than the acute ischemic stroke group (p<0.05).

Conclusions: In our study, it was observed that after acute ischemic stroke high ferritin level and low T3 is associated with worse neurological outcome and linked to the poorer results at hospital discharge.

Keywords: Stroke, Ischemic stroke, Serum ferritin, Thyroid hormones, T3

INTRODUCTION

According to the WHO, stroke is well-defined as ‘rapidly developing clinical symptoms of focal (or global) disorder of cerebral function with symptoms lasting at least 24 h or longer or leading to death, only due to vascular origin’. Stroke is among the primary cause of death in India. According to I.C.M.R., stroke and diabetes collectively caused a national economic loss of around 46 billion dollars in India during 2006 and 2015. Cerebrovascular diseases occur because of embolism or thrombotic events in the vessels supplying or draining the brain leading to ischemia. Under ischemic conditions, mitochondrial production of ATP ceases, and intracellular ATP stores deplete, resulting in cell membrane depolarization leading to a large influx of calcium and sodium and an efflux of potassium.

Ferritin and other acute-phase reactants play a significant role in ischemic stroke pathogenesis because acute cerebral ischemia activates interleukin-6 release into cerebrospinal fluid and blood, which is a crucial mediator of acute events and induces synthesis of acute-phase proteins during ischemia. Ferritin represents the iron storage in the body and needed for the synthesis of hemoglobin, cytochromes, and iron-sulfur compounds. In the brain, ferritin is localized in astrocytes and microglia,
and its concentrations increase during inflammation. Studies have suggested that iron excess contributes to the development of vascular disease by promoting thrombosis after arterial injury. A higher level of ferritin at the time of admission predicts a poor prognosis in acute stroke patients (within 24-48 h after stroke onset), implicating that increase in the body iron level before stroke onset can increase the cytotoxicity of brain ischemia. Thus, it has been postulated that a higher level of serum ferritin influences the prognosis of ischemic stroke and also acts as a risk factor for ischemic episodes by enhancing atherogenesis.

Thyroid hormones have a significant role in controlling cellular metabolic activity and neural growth. Circulating levels of thyroid hormone appear to moderate the outcome of ischemic reperfusion injury. Hypothyroidism is a probable risk factor for stroke, even though there are very few studies to prove it.

There are various indicators such as the size of the infarct, the vessel involved, the amount of edema surrounding the infarct, National Institute of Health Stroke Scale (N.I.H.S.S.), Canadian Stroke Scale (CSS), and Glasgow Coma Scale (G.C.S.) have been used to access the severity and to prognosticate acute ischemic stroke.

The aim of the current study was to assess serum ferritin and thyroid hormones level in acute ischemic stroke and their association with hemorrhagic conversion.

**METHODS**

This hospital-based prospective observational study of 60 patients has been carried out in P.G. Department of Medicine, L.L.R. and associated hospitals, G.S.V.M. Medical College, Kanpur, from July 2019 to June 2020. The study was approved by the ethics committee G.S.V.M. Medical College, Kanpur.

**Inclusion criteria**

All individuals above the age of 18 years were Patients admitted with focal neurological deficit lasting more significant than 24 hours, patients with focal neurological deficit with CT/MRI showing infarct at point of time, patients more than 18 years of age of both genders were included in this study.

**Exclusion criteria**

Patients with hemorrhagic stroke at the time of presentation, any head injury, previous stroke or intracranial hemorrhage, having an underlying medical disease that affected the level of ferritin such as anemia, treatment with iron supplements, chronic liver disease, chronic kidney disease, who consumed >40 g/day alcohol for >12 months, arterial-venous malformations, bleeding disorders, hematological malignancies were excluded from the study.

**Methodology**

An informed consent was taken either from the patient or their relatives before interview, examination, and investigation. Detailed history and physical examination were performed and recorded on predesigned proforma (annexure 1) from each patient. Patient’s personal history, physical examination findings like name, age, sex, demographic profile, height, weight, B.M.I., diet, risk factors, blood pressure, blood sugar level, diabetes mellitus duration, hypertension, E.C.G. were recorded. Proforma was prepared in English, and local language was used during the interview to make it convenient for the population.

**Hemodynamic Measurements**

For our study, pulse rate, systolic blood pressure, and diastolic blood pressure were measured, and hypertension was assessed according to JNC VIII Criteria.

**Laboratory Investigations**

Complete blood count; liver function test, kidney function test; blood sugar: fasting and post-prandial (2 hours), HbA1c; fasting lipid profile; prothrombin time studies, bleeding time/clotting time; serum ferritin: Serum ferritin’s quantitative estimation was done among the involved patients within 24 hours of presentation using the electrochemiluminescence immunoassay “E.C.L.I.A.” in Elecsys and Cobas immunoassay analyzer. The normal range for serum ferritin is 30 to 350 ng/ml.

Thyroid Hormone: By immunoassay analyzer cobas e411, Roche diagnostics, Germany.

**Table 1: Reference range.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (µUI/mL)</td>
<td>0.27-4.20</td>
</tr>
<tr>
<td>T3 (nmol/L)</td>
<td>1.2-2.7</td>
</tr>
<tr>
<td>T4 (µg/dL)</td>
<td>5.13-12.5</td>
</tr>
</tbody>
</table>

**Radiological examination**

Brain imaging, including computed tomography (C.T.) and magnetic resonance imaging (MRI), Neck vessel doppler scan, electrocardiography, and Chest X-ray were performed.

**Statistical analysis**

Data was analyzed using Statistical Package for Social Sciences, version 23 (S.P.S.S. Inc., Chicago, IL). Appropriate statistical tests were applied for data analysis, and p<0.05 considered significant. Results for continuous variables are presented as mean ± standard deviation, whereas results for categorical variables are presented as number (percentage).
RESULTS

The mean age of patients was 56.28±11.45 years, with a majority of patients of 51 - 60 years [23 (38.3%)] age group, and least was ≤40 years [4 (6.7%)]. Out of the total of 60 patients, 61.7% were male, and 38.3% were female. The mean value of serum ferritin, thyroid hormones, and Glasgow coma scale (G.C.S.) on the day of admission and on the 7th day was obtained, and the association was found to be statistically significant (p<0.05) in Serum Ferritin and T3 level while TSH and T4 shows the insignificant association (Table 2). The association of serum T3 level, serum ferritin was significant (p<0.05) but serum T4 and serum TSH level was insignificantly associated with G.C.S. levels on admission (Table 3). The Pearson correlation (r-value) analysis represents a strong statistical association between T3 and serum ferritin with G.C.S. (p<0.05), whereas for T4 and TSH, it was non-significant (>0.05) (Table 4). Out of 60, only 5 (8.3%) patients were reported as hemorrhagic conversion (Figure 1). There was no significant association was found in parameters among acute ischemic and hemorrhagic conversion patients (p>0.05) (Table 5). At admission, serum ferritin and T3 level shows a significant association (p<0.05), but TSH and T4 was insignificantly associated (p>0.05); on the seventh day of admission, serum ferritin level shows the significant association (p<0.05), but TSH, T3, and T4 was insignificantly associated (p>0.05) in acute ischemic and hemorrhagic conversion patients (Table 6). The Hemorrhagic Conversion patients were significantly greater days stay in hospital than the acute ischemic stroke group (p<0.05) (Table 7).

Table 2: Serum ferritin, thyroid hormones level, and G.C.S. on date of admission and afterwards on the 7th day.

<table>
<thead>
<tr>
<th>Variables</th>
<th>On date of admission (N=60)</th>
<th>On 7th day (N=60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ferritin</td>
<td>336.86±161.01</td>
<td>265.95±116.92</td>
<td>0.001</td>
</tr>
<tr>
<td>TSH</td>
<td>4.03±2.14</td>
<td>3.50±2.51</td>
<td>0.657</td>
</tr>
<tr>
<td>T4</td>
<td>5.59±2.00</td>
<td>5.23±2.24</td>
<td>0.355</td>
</tr>
<tr>
<td>T3</td>
<td>0.65±0.59</td>
<td>1.05±0.68</td>
<td>0.008</td>
</tr>
<tr>
<td>GCS</td>
<td>9.43±2.93</td>
<td>9.65±3.43</td>
<td>0.706</td>
</tr>
</tbody>
</table>

Table 3: Correlation of serum ferritin and thyroid hormones with G.C.S. on admission.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>G.C.S. ≤8 Mean±SD</th>
<th>G.C.S. &gt;8 Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ferritin</td>
<td>437.36±177.33</td>
<td>265.24±100.42</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>T3</td>
<td>0.69±0.63</td>
<td>1.3±0.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>T4</td>
<td>5.07±1.62</td>
<td>5.9±2.24</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>TSH</td>
<td>4.36±2.45</td>
<td>3.8±1.93</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 4: Pearson correlating thyroid profile and serum ferritin with GCS.

<table>
<thead>
<tr>
<th></th>
<th>GCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>Pearson Correlation: 0.427</td>
</tr>
<tr>
<td>T4</td>
<td>Pearson Correlation: 0.168</td>
</tr>
<tr>
<td>TSH</td>
<td>Pearson Correlation: 0.141</td>
</tr>
</tbody>
</table>

Table 5: Comparative study of parameters in both groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Acute ischemic stroke (N=55)</th>
<th>Hemorrhagic conversion (N=5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>56.55±11.72</td>
<td>53.40±10.04</td>
<td>0.564</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>168.05±16.32</td>
<td>172.80±18.09</td>
<td>0.535</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>89.45±5.62</td>
<td>90.80±6.72</td>
<td>0.616</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>133.80±30.53</td>
<td>131.60±55.18</td>
<td>0.886</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.39±1.15</td>
<td>6.38±1.81</td>
<td>0.985</td>
</tr>
<tr>
<td>Hb (gm%)</td>
<td>13.65±0.83</td>
<td>13.48±1.17</td>
<td>0.672</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>197.20±37.87</td>
<td>217.80±59.02</td>
<td>0.271</td>
</tr>
<tr>
<td>TGs (mg/dl)</td>
<td>115.84±23.93</td>
<td>102.80±17.12</td>
<td>0.240</td>
</tr>
</tbody>
</table>

Continued.
Hemorrhagic transformation of ischemic stroke is complicated. Current data has presented that low T3 levels instantly following acute ischemic stroke are related to larger stroke severity, mortality, and poorer functional outcomes. As a significant number of patients with ischemic stroke are transferred for inpatient rehabilitation, hemorrhagic transformation may be detected during this period. Hemorrhagic transformation may also affect the decision of restarting anti-platelets or anticoagulants, and thus the factors which contribute to hemorrhagic transformation are essential. This particular group of patients should be monitored carefully for neurological deterioration and undergo serial brain scans.

The current prospective observational study was done. Similar studies were performed by Mandal et al, Koul et al, Mehrpour and Miharpour conducted a prospective cohort study that concluded that the level of serum ferritin is greater than 164.1ng/ml in the first 24 hours after admission is a reasonably important predictor for hemorrhagic transformation of ischemic stroke. Pandey et al studied the thyroid dysfunction in patients of ischemic cerebrovascular accidents and concluded the levels of free T3 were linked with hemorrhagic transformation with ischemic stroke and stroke recovery.

**DISCUSSION**

Iron plays a vital role in neurotoxicity and edema formation after stroke. Hemoglobin degradation releases iron after erythrolysis, and iron is also released from ferritin stores and is extremely neurotoxic by catalyzing hydroxyl radical formation and stimulating oxidative stress.2

The relationship between thyroid hormones and functional outcomes post-stroke is complicated. Current data has presented that low T3 levels instantly following acute ischemic stroke are related to larger stroke severity, mortality, and poorer functional outcomes. As a significant number of patients with ischemic stroke are transferred for inpatient rehabilitation, hemorrhagic transformation may be detected during this period. Hemorrhagic transformation may also affect the decision of restarting anti-platelets or anticoagulants, and thus the factors which contribute to hemorrhagic transformation are essential. This particular group of patients should be monitored carefully for neurological deterioration and undergo serial brain scans.
In our study, the mean age of patients was 56.28±11.45 years. Pandey et al reported the 68.4±11.5 years in their study. Paciaroni et al reported the mean age of their study patients was 76.1±9.8 years. Male patients were in the majority (61.7%), whereas females were (38.3%) in the present study. Similarly, O’Keefe et al also reported the 60.5% male and 39.5% female in their study.  

In our study, the ischemic stroke in 55 (91.7%) remain ischemic while 5 (8.3%) patients shown the hemorrhagic conversion. Aviv et al reported the hemorrhagic transformation of Ischemic Stroke (is a comparatively frequent complication going on in 2.2% to 44% of clinical cases. Dzialowski et al reported the hemorrhagic transformation is associated with poor diagnosis of patients with ischemic stroke. Also, it is one of the core obstacles for the on-time start of thrombolytic therapy. Some known risk factors for hemorrhagic transformation suggested by Aviv et al, Kerenyi et al, and Lindley et al. studies are the severity of ischemic stroke, history of diabetes mellitus, old age, the time to reperfusion, thrombolytic therapy, use of Aspirin and other anticoagulant drugs. Millan et al and Choi et al studies revealed that the level of serum ferritin could be a novel predictor for hemorrhagic transformation. 

Serum Ferritin and T3 level shows a significant association (p<0.05), but TSH and T4 was insignificantly associated (p>0.05). Bayir et al reported that in patients with hemorrhagic stroke, high TSH levels were observed within the first 3 hours of stroke onset, which could be considered an indicator of poor prognosis.  

In our study, serum ferritin level shows significantly higher hemorrhagic conversion than the ischemic stroke (p<0.05). Pandey et al study showed an increased level of serum ferritin in acute ischemic stroke patients compared to normal individuals, which is in agreement with Emre et al and Balachandiran et al study conducted in their population. Numerous mechanisms may describe the vital role of ferritin in ischemic stroke. Free radicals are produced in improved amounts under ischemic conditions that respond with and damage proteins, nucleic acids, and membrane lipids, disrupting cellular integrity. This oxygen radical activity is especially intense during reperfusion after sustained ischemia. The generation of hydroxyl radical is catalyzed by ferrous iron released from ferritin during ischemia. Monica Millan et al. reported the increased body iron stores are associated with poor outcome, symptomatic hemorrhagic transformation, and severe edema in patients treated with tissue plasminogen activator after ischemic stroke. Kaushik et al reported the higher level of serum ferritin (within the normal physiological range) is correlated with higher conversion to hemorrhagic transformation in acute ischemic stroke patients and can be used as a predictor. 

Davalos A et al. and Erdemoglu AK et al. illustrated that the high serum ferritin level in the patients with ischemic stroke at the first 24 hours of admission was related to growth of the size of the lesion, the severity of stroke, and poor prognosis. 

In our study T3 level shows a significantly lower in the hemorrhagic conversion group than the ischemic stroke (p<0.05). Alevizaki et al. discovered that a high number of patients with acute stroke were noticed to have low T3 levels just after the event and low T3 syndrome is a free predictor of early and late survival in such patients. Rahman HA et al. reported that in patients with acute ischemic stroke, lower T3 level elevated the risk of poor functional outcome. 

Multivariate logistic regression analysis also found a statistically significant correlation of T3 level and serum ferritin level with G.C.S. score. Huang GQ et al. reported the multivariate logistic regression displayed that low T3 syndrome was an independent risk factor for hemorrhagic transformation and symptomatic hemorrhagic transformation in acute ischemic stroke patients. Wang Y et al. reported the regression analyses revealed that lower tri-iodothyronine concentrations on admission were associated with a risk for poor outcomes (p<0.01). 

Hemorrhagic Conversion patients were significantly greater days of stay in hospital than the acute ischemic stroke group (p<0.05). The hemorrhagic conversion patients had greater serum ferritin levels and lower T3 levels than the ischemic stroke patients. Due to this, there was poor functional recovery after ischemic stroke. 

Limitations of this study where the small sample size and short time of follow-up. Furthermore, because ferritin is an acute-phase reactant, so many confounding conditions affect its serum level. Hence, it was impossible to eliminate all factors affecting serum ferritin level despite our extreme efforts, limiting the understanding of our findings. Conducting multi-centric researches with long-term follow-ups and bigger sample sizes is extremely recommended. 

Strengths of the study was our findings show real-life experiences and, given a single-center Hospital-based prospective study, may provide info that could help stroke physicians manage the patients having acute ischemia with hemorrhagic conversion. 

**CONCLUSION**

Our study supported earlier studies’ findings, which found that serum ferritin level was a predicting factor for hemorrhagic transformation of ischemic stroke. Consequently, the serum ferritin level of greater than 350 ng/ml in the first 24 hours after admission of the patients with acute ischemic stroke can be considered for more attention when dealing with these patients, particularly during anticoagulant and thrombolytic therapy. Our study shows that low T3 after acute ischemic stroke is associated with worse neurological outcomes and is connected to poorer hospital discharge outcomes.
ACKNOWLEDGEMENTS

The authors would like to thank all the esteemed members of the Medicine department of G.S.V.M. Medical College for their invaluable contribution and support throughout the research. The authors would also like to thank all the patients and their family members who cooperated during the entire research.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES


