Correlation Between Ferritin Level Serum And Clinical Outcome On Acute Ischemic Stroke

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Abstract

Ferritin is an acute phase reactant and is likely to increase in conditions of infection or inflammation both acute and chronic. When an ischemic stroke occurs, a state of oxidative stress occurs so that free iron is released. Oligodendrocyte cells form ferritin to capture free iron ions. High levels of ferritin in stroke patients are associated with poor clinical outcomes. A cross-sectional analytic observational study from January to May 2019. Information gathering was carried out by taking data from medical records, neurological physical examinations, NIHSS at admission, and examining serum ferritin levels when patients entered the hospital. NIHSS was also examined 7 days later. The total subjects of the study were 73 patients consisting of 38 men and 35 women with an average age of 56.11 years. The most common risk factors we found in this study were hypertension (87.7%) and dyslipidemia (87.7%). The median NIHSS value at entry was 6 (range 1-8). The median NIHSS value on day 7 was 3 (range 0-12). Median serum ferritin levels at admission were 150.40 ng / mL (range 4.7 - 646.2 ng / mL). There was a significant correlation between serum ferritin levels with incoming NIHSS ($r = 0.250$, $p = 0.033$) and the onset 7-day NIHSS ($r = 0.253$, $p = 0.031$). There was a correlation between serum ferritin level and NIHSS score at the beginning of entry and the 7th day of onset of acute phase stroke.

INTRODUCTION

The World Health Organization (WHO) defines stroke as a clinical sign of focal and global cerebral dysfunction that lasts more than 24 hours or causes death, and is solely caused by vascular disorders. When an ischemic stroke occurs, a state of oxidative stress occurs so that free iron is released. Oligodendrocyte cells respond to the amount of free iron by forming ferritin, which initially aims to help bind to free iron and prevent peroxidation. The occurrence of oxidative stress also damages the blood brain barrier, so that free iron and free radicals in the plasma can enter the ischemic area and expand the ischemic area (Bishop GM, 2001)

Ferritin which was originally formed a lot, became a negative role in the penumbra area. The iron ion in ferritin is released into the cytoplasm because of the many free radicals in the area. As a result of cell membrane damage during ischemic events, ferritin which has lost a lot of iron will be released from the cytoplasm into the serum. The wider the ischemic area, the greater the oxidative stress that occurs and the more ferritin is formed. High levels of ferritin in stroke patients are associated with poor clinical outcomes (neurological deficits), this can be seen by the NIHSS (National Institutes of Health Stroke Scale) score (Erdemoglu, 2002)

We hypothesize serum ferritin level is related to clinical outcome of ischemic stroke based on NIHSS score.

METHOD

A Cross-sectional study of acute ischemic stroke from January 2019 to May 2019 which have been performed head CT scan without contrast, NIHSS assessment (on admission and on the 7th day of stroke onset), and serum ferritin levels were examined on admission <24 hour. Patients with complications that may interfere with ferritin levels such as respiratory failure, acute kidney failure, acute myocardial infarction, acute ischemic limbs, malignancy, blood disorders (anemia, thalassemia, leukemia, hemophilia), acute infections, hypothyroidism, family history of excess limb iron, patients who were also alcohol users, iron supplement users, had a previous blood transfusion, and menstruation upon hospital admission were not included in the study.

Statistics was calculated with Spearman rank test using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA). $p<0.05$ was considered statistically significancy, r squared is calculated for correlation.

RESULTS

There were 73 patients who had CT head scans 24 hours after stroke onset and serum ferritin levels within 24 hours after admission. Fifty-two point one percent are men and 47.9% are women. The average age is 56.11 years (range 21 to 78). The most common risk factors we found in this study were hypertension (87.7%) and dyslipidemia (87.7%). (table 1)

Table 1

Characteristic of research subjects

Variable		Value
Age		
Mean ± standard deviation	years	56.11 ± 9.201
Range	years	21-78
Gender		
Male (n, %)		38 (52.1%)
Female (n, %)		35 (47.9%)
Risk factor		
Hypertension (n, %)		64 (87.7%)
Diabetes mellitus (n, %)		18 (24.7%)
Dyslipidemia (n, %)		64 (87.7%)
Hyperuricemia (n, %)		11 (15.1%)

The median NIHSS value at entry is 6 (range 1-8). The median ASPECT score is 8 (range 5-9). The median value of NIHSS on the 7th day of admission is 3 (range 0-12). Median serum ferritin levels at admission were 150.40ng / mL (range 4.7 - 646.2 ng / mL). All of this data is listed in table 2.

Table 2

Distribution of ferritin and NIHSS

Variable	Median (Min-Maks)
Serum feritin level (ng/mL)	150.40 (4.7 – 646.2)
NIHSS on admission	6 (1-18)
NIHSS 7th day of stroke onset	3 (0-12)

Table 3 shows the relationship between serum ferritin levels and NIHSS. There was a weak positive correlation between serum ferritin levels at admission and NIHSS at admission ($r = 0.250$; $p = 0.033$) and on the 7th day after stroke onset ($r = 0.253$; $p = 0.031$).

Table 3

Bivariat analysis ferritin level serum and NIHSS

Variable	Serum ferritin level (ng/mL)	
	Coefisien r	P value
NIHSS on admission	0.250	0.033*
NIHSS 7th day of stroke onset	0.253	0.031*

*statistically significance

DISCUSSION

Ferritin is present in most body cells in the form of cytosolic proteins. Ferritin in serum contains mostly iron and is believed to be glycosylated. Ferritin is secreted by hepatocytes, macrophages, and Kupffer cells (Wang et al, 2010).

Extracellular ferritin functions as an iron carrier capable of carrying up to 4,500 iron atoms, but in general each ferritin contains only 1,000 - 1,500 iron atoms. Extracellular ferritin requires receptors on the cell surface to bind. Specific cells bound to ferritin include liver cells, oligodendrocytes, enterocytes, and erythroid precursor cells (Kell DB, 2014).

The bond between extracellular ferritin and receptors on the surface plays an important role in the pathway of iron delivery in the brain. Iron itself is needed by oligodendrocytes to produce myelin. Ferritin H receptors on the surface of oligodendrocyte cells take ferritin by endocytosis (Wang et al, 2010).

Strokes cause an increase in superoxide free radicals, so the amount of iron ions in the cytosol increases during oxidative stress. Free iron in the cell or the so-called labile iron pool (LIP) becomes a sensor for homeostastic iron in the cell. When the iron in LIP increases, iron acts as a source of iron for the Fenton reaction. The brain's oxygen demand increases when ischemia occurs, resulting in an increase in the need for iron transport and its use in certain areas. The exact source and form of iron ions released during cerebral ischemia have not yet been fully identified. There are several possible disorders of iron balance in the brain after ischemic stroke, including interruption in transferrin, ferritin, or transitional iron ions (Selim EH, 2004)

Although the mechanism is unclear, it is thought that the decomposition activity of iron-containing proteins in lysosomes plays a role in the removal of iron ions. Iron can be released from its binding with storage proteins in the brain in the event of hypoxic conditions (Sorrond, 2000) These free iron ions will oxidize fat in the cell membrane and provoke an inflammatory response and glutamate

excitotoxicity (Selim EH, 2004; Choi KH et al. , 2012)

We hypothesize that there is a correlation between iron levels with a pathophysiological mechanism that leads to neuronal injury and the level of infarction and penumbra area after ischemic stroke. The level of infarction and the penumbra area is related to the severity of neurological deficits. We found a positive correlation between serum ferritin levels at admission and NIHSS in this study.

In cerebrovascular disease, the presence of superoxide oxygen radicals increases the amount of iron in the cytosol by releasing iron from ferritin (Carbonell, 2007; Sorrond, 2000; Selim KH, 2004). Hypoxia-ischemic state induces expression of ferritin in oligodendrocytes and microglia (Bishop GM, 2001). When oxidative stress occurs, the formation of ferritin will increase (Carbonell, 2007).

Most of the stimulus associated with inflammation will cause an increase in ferritin production. This is related to high levels of nitric oxide (NO) which will encourage the formation of ferritin indirectly (Arosio, 2002).

High levels of iron in cells are toxic to the cells themselves. This free iron can start and spread lipid peroxidation so that the cell membrane is disturbed. The disrupted cell membrane causes cellular edema which ultimately causes damage to neuronal cells (Carbonell et al, 2007)

To overcome the excess intracellular iron, the body has several defenses, one of which is by forming a reservoir for free iron, because there are not many superoxide dismutase enzymes in the central nervous system that can clean up free radicals (Frosch MP, 2015). The main iron reservoir in cells is ferritin (Lo EH, 2003)

High levels of intracellular iron encourage ferritin mRNA to be translated into ferritin. However, when ischemic occurs, ferritin that has formed will be degraded due to the presence of peroxide and ferritin will enter the bloodstream due to blood-brain barrier damage (Sacco et al, 2013; Carbonell et al, 2007)

In this study, a weak positive correlation was obtained between serum ferritin levels and NIHSS score at the time the patient was first admitted to the hospital ($r = 0.250$, $p = 0.033$). This result is in line with many previous studies. Davalos et al in 1994 showed that high serum ferritin levels in the first 24 hours since the onset of a stroke were associated with a poor prognosis. Studies in 2015 and 2016 in Kanpur and Vellore, India show that serum ferritin levels have a significant positive correlation with NIHSS and Canadian Stroke Scale (CSS) when patients are hospitalized (Gracia YI, 2012). Erdemoglu and Ozbakir have compared serum ferritin levels and lesion areas based on their visualization on CT-scan (small lesions with a diameter of 5mm, large lesions covering one vascular region, or medium lesions in between) and CSS scores in 2002. This study shows that there was a positive correlation between serum ferritin levels and lesion levels, and the severity of neurological deficits. In patients with extensive lesions, serum ferritin levels were higher (378.4 ± 51.2 ng.mL) compared to the area of moderate lesions (209.0 ± 33.9 ng.mL) and small lesions (146.7 ± 20 , 8 ng.mL). All of this research shows that serum ferritin is an objective marker of neurological deficits in patients with acute ischemic stroke.

The NIHSS assessment on day 7 since the onset of a stroke is a sensitive assessment method for determining the prognosis in patients with acute stroke according to Kerr, et al. There are no studies comparing day 7 of a NIHSS stroke with serum ferritin levels. The NIHSS score on day 7 in this study had a weak positive correlation with serum ferritin levels. The higher the serum ferritin level, the higher the NIHSS score. These results indicate that serum ferritin levels at the time the patient is hospitalized can be one of the benchmarks for assessing patient outcomes.

The limitation of this study is the absence of data on serum ferritin levels before the onset of a stroke. This situation is one of the weaknesses in this study because it is not known for certain whether serum ferritin levels in these patients increased, were equal, or even decreased during the event of a stroke.

CONCLUSION

Based on this study, serum ferritin levels can describe the level of neurological deficits of acute ischemic stroke patients on admission and day 7 after the onset of a stroke. This can be an objective value for doctors in determining the severity of neurological deficits in stroke patients. The doctor also needs to consider if the patient has a disease or other condition that causes an increase in serum ferritin, then the serum ferritin level cannot be used as an objective value for the patient's neurological deficit.

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