Frequency of Iron Deficiency Anemia in Ischemic Stroke

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Abstract

Objective: To determine the frequency of iron deficiency anemia in ischemic stroke.
Methods: Total 200 patients with ischemic stroke were included. Investigations including Hemoglobin, Mean Corpuscular Volume (MCV), MeanCorpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) serum iron level, and serum ferritin level, Total Iron Binding Capacity (TIBC), White Blood Cell (WBC) count andplatelets count (PC) were done. CT scan of brain was also done.Mean±SD were evaluated for quantitative variables which were distributed normally. However, median with inter-quartile range were evaluated for quantitative variables which were non-normally distributed. Data was compiled using SPSS version 25. To check normality of data, Shapiro-Wilk test was applied. To compare the association of qualitative variables, Chi-square test was used. Pvalue ≤ 0.05 was considered as statistically significant.
Results: In our study, out of 200 patients having ischemic stroke, 156 (78%) patients were found with iron deficiency and 44 (22%) did not have iron deficiency. Total 164 (82%) patients were anemic and 36 (18%) did not have anemia. The results showed significant mean ranks for Ferritin ($p<0.001$), Iron ($p<0.001$), Hemoglobin($p<0.001$), Mean Corpuscular Volume($p<0.001$), Mean Cell Hemoglobin ($p<0.001$), Mean Corpuscular Hemoglobin Concentration ($p<0.001$), and Total Iron Binding Capacity ($p=0.005$) with respect to iron deficiency, however White Blood Count ($p=0.417$) and platelet counts ($p=0.511$) did not have significant mean rank with respect to iron deficiency. As far as anemia is concerned, significant mean ranks was observed for Ferritin ($p=0.002$), Iron ($p<0.001$), Hemoglobin ($p<0.001$), Mean Corpuscular Volume ($p<0.001$), Mean Cell Hemoglobin ($p<0.001$), and Mean Corpuscular Hemoglobin Concentration ($p<0.001$). However, white blood count ($p=0.270$), platelet counts ($p=0.320$), and Total Iron Binding Capacity ($p=0.535$) did not have significant mean rank. .A significant association of iron deficiency with anemia ($p<0.001$) was also observed
Conclusion: Study results show thatsignificant number ofischemic stroke patients have iron deficiency anemia.
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Introduction

A stroke is a sudden reduced function of brain that isbrought on by a disruption in blood flow to the brain.Stroke may have been caused by a hemorrhage or ischemia[1]. Stroke is the neurological deficiency caused by vascular source, such as cerebral infarction or intracerebralhemorrhage, which causes an immediate focused insult to the central nervous system.Stroke is regarded as the 2nd largest reason for death and the one among worldwide main reasons of protracted disability[2]. While western society's mortality trends are falling, changes in the incidence of stroke are not keeping pace. According to the Global Burden of Disease in the years 2016, lifetime risk of stroke among population with age 25 years or more was 24.9%, as compared to 22.8% in1990[3]. Globally, because of its complicated nature, the ischemic stroke (IS) was considered as one of the main reasons that causes morbidity and disability. Several biomarkers and risk variables have been successfully found using

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various methodologies. The association of anemia with ischemic stroke may be partly explained with the help of establishing a direct link between the central nervous system (CNS), blood supply, and tissue oxygenation.Hemoglobin (Hb), the major content of red blood cellsin the blood that carry-oxygen, must be crucial for the fate of the penumbral region or have an impact on brain healing and neurologic function, which might change the ischemic stroke outcomes[4].

Anemia occurs when the red blood cell counts or hemoglobin concentration are below their normal levels. Anemia is a major medical problem and a prevalent condition among the elderly, with its frequency increasing with age[5]. Red blood cells (RBCs) or hemoglobin levels in the blood fall during anemia. Blood loss is the most frequent cause of anemia, although other factors including inadequate RBC generation or excessive RBC breakdown may also contribute[6]. Anemia and iron deficiency are frequent co-morbidities in older patients with cardiovascular disease[7,8] and they have a significant negative influence on muscle health and athletic capacity.

Iron deficiency anemia (IDA) is characterized by reduced red blood cell formation due to less than normal reserves of iron in the body. Iron is required for several physiological activities, including erythropoiesis, oxidative metabolism, and immunity. IDA is the most frequent cause of anemia worldwide.

The most prevalent blood illness, anemia, has been linked in a significant way to both cerebrovascular and cardiovascular conditions[9]. Only the sickle cell anemia subtype was shown to have a strong correlation with CVA. Although it appears that the pathogenesis of stroke or other morbidities in sickle cell anemia is complex and distinct among more frequently observed IDA. According to mounting evidence, underlying molecular and genetic processes are responsible for these events (IDA) [1].

Low hemoglobin levels have been implicated as a cause of unfavorable outcomes as well as decreased survival. Anemia is connected to a poorer prognosis in patients with acute ischemic stroke (AIS).Uncertainty exists about the precise relationship between hemoglobin levels and the prognosis following AIS. It is assumed that both high and low hemoglobin levels are associated with subpar outcomes. Every fifth AIS patient has low hemoglobin levels, which are thought to have a poorer neurological outcome[2].

Many observational studies have discovered a link between a drop in iron levels and a higher risk of stroke. Pakistan has a high stroke rate. Pakistan carries a substantial portion of this crippling burden, contributing to an exponential consumption of resources, community personnel, funds, healthcare workers' services, and the economy as a whole.Our study was designed to focus on the relationship between low hemoglobin levels secondary to iron deficiency and stroke. The ultimate result will help to raise awareness of the burden of stroke, which may help with patient care, increase access to healthcare, and lead to better outcomes[3].

In a study, the results revealed a roughly similar risk of stroke in men and women, as well as an 18.3% risk of ischemia-related stroke and an 8.2% risk of hemorrhagic stroke[3].Conflicting data support the link between iron status and the risk of stroke. While some research show a relationship between greater iron status and an increased risk of stroke, other observational studies have established a cor-relation between low iron levels and an increased risk of stroke[10]. Additionally, several studies found no associationbetween iron status and the risk of stroke[11].

An observational research found that anemia at the time of admission increased the risk of mortality during long-term follow-up in patientswith ischemic stroke. In a meta-analysis of longer-term observational studies, mortality risk for both ischemic and hemorrhagic stroke increased when anemia was present[6].

It was also reported in literature that anemia and iron deficiency can be risk factors to causeweakened muscles, early weariness, low quality of

life, extended hospital stays, and decreased survival. A history of iron deficiency anemia was more common in patients with ischemic stroke than in those without ischemic stroke[9]. Lower blood iron content is indicative of decreased iron transport and negative iron balance and hence islinkedwith enhanced risk of stroke in the elderly patients. The highest quartile of total iron binding capacity is a characteristic that rises with iron shortage and was found to have an elevated risk of stroke[12].

Over the years, a number of stroke risk calculators have been created, but none of them incorporated iron deficiency Anemia (IDA). There are variety of suggested theories underlying the pathophysiology of anemia-related strokes. First, anemia results in hyperdynamic condition that compromises the endothelium lining, increasing the probability of thrombus formation as per Virchow's triad and dislodging the clot-producing arterial embolic strokes. Second, anemia, particularly iron deficiency anemia, has higher platelet levels which in turn leading to hypercoagulable state. Third, impaired oxygen delivery to tissues is caused by altered red blood cell deformability[12].

This study was planned with the aim that sinceiron deficiency anemia is an easily treatable condition and if a link is found between it and ischemic stroke, thenby treating iron deficiency anemia, one of the causes of stroke can be eliminated.

Patients and Methods

In the current study we had included total 200 patients with either gender having age between 30 to 80 years. Current study is a cross-sectional study which was carried out during the period from January to June in the year 2022. The study was conducted after taking approval from Institutional Review Board. Before inducting the study participants, all participants werebriefly explained about purpose of the current research. Aninformed consent was taken by each included participant. By using Spss version 11 test for one sample population, 95% confidence interval, 80% power of test, 5% margin of error and 74% (37/50) prevalence of iron deficiency anemia with stroke patients within 6 months, sample size of 200 was calculated. Consecutive non-probability sampling method was used for data collection. Patients who were admitted in Dow University Hospital with ischemic stroke presented within 72 hours of commencement of sign and symptoms were included in the study. Patients were enquired about demographic details, past medical history, risk factors and duration of symptoms. Blood was taken for laboratory investigations like Hemoglobin, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) serum iron level, and serum ferritin level, Total Iron Binding Capacity (TIBC), White Blood Cell (WBC) count andplatelets count. In addition to this CT scan of brain was also done. Mann Whitney U test was applied for comparison. Patients with stroke other than ischemic stroke, having hemoglobinopathies and mentally retarded subjects were not included in the study. Data was compiled using SPSS version 25. The Qualitative variables of the study were evaluated and presented in-terms of frequency and percentage while mean and standard deviation were determined for normally distributed quantitative variables whereas non-normally distributed quantitative variables were evaluated and summarized in-terms of median with inter-quartile range. The Shapiro-Wilk test was used to test the assumption of normality in quantitative variables. To compare categorical variables among study patients Chi-square test was applied. P-value less than or equal to 0.05 was taken as statistically significant.

Results

There were 124 (62%) males and 76 (38%) female patients in our study. As the data has not followed the normality assumption, so median and IQR were reported. The median age of patients was 58 years with a range from 34 years to 80 years. The majority of patients 146 (73%) have age more than 50 years however, 54 (27%) patients belonged to age 50 years or less. In our study, 156 (78%) patients were found with iron deficiency and 44

(22%) did not have iron deficiency. Among the patients with iron deficiency95 (60.9%) were male and 61 (39.1%) patients were female. As far as age groups are concerned, 39 (25%) patients who were observed with iron deficiency belonged to age 50 years or less and 117 (75%) patients with iron deficiencybelonged to age more than 50 years.

Total164 (82%) patients were observed to have anemia, however 36 (18%) did not have anemia. Among anemic patients, 100 (61%) were male and 64 (39%) patients were female. It was observed that among anemic patients 43 (26.2%) patients belonged to age 50 years or less and 121 (73.8%) patients belonged to age more than 50 years. The detailed results are also presented in Table-1.

Table 1. Association of gender and age with iron deficiency and anemia in ischemic stroke patients

	Totaln (%)	**Iron Deficiency**			**Anemia**		
	n(%)	Yes n(%)	No n(%)	p-value	Yes n(%)	No n(%)	P-Value
Gender							
Male	124(62)	95(60.9)	29(65.9)	0.545	100(61)	24(66.7)	0.524
Female	76(38)	61(39.1)	15(34.1)		64(39)	12(33.3)	
Age Group							
≤50 years	54(27)	39(25)	15(34.1)	0.230	43(26.2)	11(30.6)	0.596
>50 years	146(73)	117(75)	29(65.9)		121(73.8)	25(69.4)	

The overall range, median, and inter quartile range (IQR) of quantitative variables were evaluated. The results showed that median (IQR) of Ferritin was 15.00(11) ng/ml, Iron was 40.00(39) mcg/dl, Hemoglobin (Hb) was 9.00(2.90) g/dl, Mean Corpuscular Volume (MCV) was 70.00 (13.75) fl, Mean Cell Hemoglobin (MCH) was 23.00 (6) pg., Mean Corpuscular Hemoglobin Concentration (MC HC) was 29.00(6) g/dl, White Blood Cells (WBC) was 9.00(3.78) $x10^9$/L, Platelet Count (PC) was 349.50(220.75)$\times10^9$/L, and Total Iron Binding Capacity (TIBC) was 467.00(241.50) ìg/dL. The overall comparison of quantitative variables according to iron deficiency and anemia was done and because quantitative variables are not following normality so Mann Whitney U test was applied for comparison. The results showed median (IQR) of Ferritin, Iron, Hemoglobin, MCV, MCH, MCHC, TIBC were 12(10), 31(33), 8.85(3), 68(13), 23(27), 28(5), 479 (238) respectively in iron deficient patients while these values are 176 (163.7), 59(77), 10(4), 78 (20.75), 27(7.75), 33(5.75), 304(215.5) respectively in non iron deficient patients respectively. Hence showing significant mean ranks for Ferritin ($p<0.001$), Iron ($p<0.001$), Hemoglobin ($p<0.001$), Mean Corpuscular Volume ($p<0.001$), Mean Cell Hemoglobin ($p<0.001$), Mean Corpuscular Hemoglobin Concentration ($p<0.001$), and Total Iron Binding Capacity ($p=0.005$) with respect to iron deficiency however While Median and IQR of White Blood Cell counts and Platelets Counts were 9 (3.8) and 349.5 (215) in iron deficient patients while 8.9 (2.95) and 350 (221) in non iron deficient anemic patients showing that White Blood Count ($p=0.417$) and platelet counts ($p=0.511$) did not have significant mean rank with respect to iron deficiency.

As far as anemia is concerned, significant mean ranks was observed for Ferritin ($p=0.002$), Iron ($p<0.001$), Hemoglobin ($p<0.001$), Mean Corpuscular Volume ($p<0.001$), Mean Cell Hemoglobin ($p<0.001$), and Mean Corpuscular Hemoglobin Concentration ($p<0.001$). However, white blood count ($p=270$), platelet counts ($p=0.320$), and Total Iron Binding Capacity ($p=0.535$) did not have significant mean ranks.The detailed results are also presented in Table-2. A significant association of iron deficiency with anemia in ischemic stroke patients ($p<0.001$) was also observed and presented in Table-3.

Table 2. Comparison of laboratory markers according to iron deficiency and anemia in ischemic stroke patients

Parameters	Range	Overall Media n (IQR)	Iron Deficiency Yes Media n (IQR)	Iron Deficiency No Media n (IQR)	p-value	Anemia Yes Media n (IQR)	Anemia No Media n (IQR)	P-Value
Ferritinng/ml	5 to 503	15.00 (11)	12.00 (10.00)	176.00 (163.75)	< 0.001	15.00 (10.75)	20.00 (147.00)	0.002
Ironmcg/dl	3 to 300	40.00 (39)	31.50 (33.75)	59.00 (77.00)	< 0.001	30.00 (30.50)	137.00 (49.00)	< 0.001
Hbg/dl	3 to 17	9.00 (2.90)	8.85 (3.00)	10.25 (4.00)	< 0.001	8.55 (2.60)	14.00 (2.00)	< 0.001
MCVfl	50 to120	70.00 13.75)	68.00 (13.00)	78.00 (20.75)	< 0.001	68.00 (11.00)	92.00 (6.00)	< 0.001
MCHpg	18 to 34	23.00 (6)	23.00 (5.75)	27.00 (7.75)	< 0.001	23.00 (5.00)	30.00 (2.00)	< 0.001
MCHCg/dl	22 to 38	29.00 (6)	28.00 (5.00)	33.00 (5.75)	< 0.001*	28.00 (4.75)	35.00 (1.75)	< 0.001
WBC10^{9}/l	4 to 22.9	9.00 (3.78)	9.00 (3.80)	8.90 (2.95)	0.417	8.80 (3.80)	9.45 (3.78)	0.270
PC10^{9}/l	107 to 560	349.50 (220.75)	349.50 (215.50)	350.00 (221.00)	0.511	357.50 (215.50)	279.50 (225.75)	0.320
TIBCmcg/dl 0.535	147 to 608	467.00 (241.50)	479.00 (238.25)	304.50 (237.00)	0.005*	470.00 (237.00)	429.50 (251.50)	

Table 3. Association of iron deficiency with anemia in ischemic stroke patients

Anemia	Iron Deficiency Yesn (%)	Non (%)	P-Value
Yes	136(87.2)	28(63.6)	<0.001*
No	20(12.8)	16(36.4)	

Discussion

Stroke is a worldwide health issue and iron deficiency anemia (IDA) is the most common cause of anemia. IDA affects between 2% and 5% of teenage girls and women of reproductive age.IDA typically manifests in women of reproductive age as a result of menstruation, which causes a gradualblood loss that occurs over time and enables the body to adjust to low hemoglobinlevels. However, when loss of blood happens suddenly, this may cause a fast decrease of blood reserves and leadsto ischema[13].

A study reported a group ofsix ischemic stroke or venous thrombosis children following a viral prodrome, and thefindings supported the results of a significant link between ischemic events and iron deficiency. Subedi et al. in his study evaluated a child with age 4 years suffering from iron deficiency anemia attributed to ischemic stroke. In his study he observed that level of hemoglobin was 7.2 g/dl on presentation[14].

The current study was conducted with the aim to determine the frequency of iron deficiency anemia among patients presenting with ischemic stroke.Most of the patients (78%) had iron deficiency and anemia (82%). Ferritin level, Hb, MCV, MCH, MCHC, and TIBC were observed as a significant parameters for iron deficiency.

Previous research has identified significant iron deficiency anemia as the primary cause of anoxic brain damage. However, previous cases have usually been linked to a major recognized source of bl-

eeding, resulting in systemic hypoperfusion or a coexisting thrombus or thrombocytosis with evidence of emboli[15].

WHO defines anemia as Hb levels below 12 g/dl for women and below 13 g/dl for men[16,17] and iron deficiency anemia is the most common type[17,18] .Studies have shown that iron deficiency anemia (IDA) has been suggested as etiological factor for ischemic stroke[19]. Iron loss by bleeding from different sites (including the intestinal, uterine, or urinary system), inadequate intake of food, and inadequate iron absorption are the main causes of the condition.

The connection between the IDA and stroke was seldom examined, despite the fair supposition that a reduction in hemoglobinmay possibly compromisethe ability of blood to carryoxygen and therefore increasecardiovascular or cerebrovascular disorders risk[1]. The first time IDA and obvious throm-bocytosis were discovered in a patient who was developing right hemiparesis and aphasia was in 1983 by Alexander et al[20], and few years later, another instance of cerebral infarction was discovered, and it was assumed that the thrombocytosis was caused by the IDA[1].

The potential causes of the IDA as a risk factor for ischemic stroke might be explained by the fact that a drop in blood hemoglobin levels would probably affect tissue oxygen supply. IDA has already been indirectly implicated in a number of studies as a risk factor for ischemic stroke.The secondary thrombocytosis brought on by iron deficiency is another potential mechanism that might help to explain the link between IDA and stroke[20]. The results of a study showing an association between the IDA and both thrombotic and embolic ischemic stroke further corroborate this theory[1].

A greater iron status has been linked to an increased risk of stroke in several observational studies[8]. On the other hand, several studies have shown association between an increased risk of stroke and an iron deficit[19].

According to a study by Heo Jet al[6], having anemia increases the probability of having an ischemic stroke by around 1.6 times within a year and 1.35 times within two years. It was also reported by Heo J et al[6], that within a year after diagnosis of anemia, there was a greater chance of developing an ischemic stroke.

Natio H et al reported 2 cases of ischemic stroke secondary to iron deficiency anemia because of bleeding from fibroid[22.]

According to other research, patients with a trend toward falling hemoglobin levels have a substantially higher chance of developing an ischemic stroke than those with stable hemoglobin levels that show no change[23]. The most prevalent anemia in the world, iron deficiency anemia, has been linked to ischemic stroke in earlier research[6]. According to a research, anemicpatients with age over 50 years had a slightly increased chance of developing an ischemic stroke than those of under 50 years. Like other comorbidities, anemia can increase the risk of ischemic stroke in younger people.

There are a few limitations of this study. The current study's limited sample size was viewed as a drawback. Because just one healthcare facility in an urban setting was used for the study, the findings cannot be applied to other clinical settings.

Conclusion

This study showed that a significant number ofischemic stroke patients have iron deficiency-anemia. To lower the risk of ischemic stroke in the future, it is suggested that patients with IDA receive more aggressive treatment for iron deficiency.

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