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Original Article

Prevalence of Iron Deficiency Anaemia in Ischaemic Stroke

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Abstract

Background:
Iron Deficiency Anaemia has been proposed as a risk factor for developing ischemic stroke. In long-term follow-up studies, and it is also known to increase the risk of death. Very little is known about the prevalence of Iron Deficiency Anaemia (IDA) in Bangladeshi stroke patients. We aimed to determine the prevalence of IDA among admitted patients of acute ischemic stroke in a tertiary care hospital in Bangladesh. ***Materials and methods:*** *In this cross-sectional study, 75 patients with acute ischemic stroke were selected purposively from the Neurology & Medicine Department of Comilla medical college hospital from February 2021 to May 2021. Traditional risk factors for stroke, stroke type and severity at admission were recorded for each patient. Anaemia is defined as haemoglobin <12gm/dl in women & <13gm/dl in men. IDA was defined as serum ferritin level <20 µgm/L in males and <40 µgm/L in females.* ***Results:*** *Mean age was 65.8 (±11.4) years. Sixty percent of patients were male. Hypertension was the most prevalent risk factor present in 73.3% of the cases, followed by diabetes mellitus (49.3%), smoking (28.0%), ischaemic heart disease (25.3%), and dyslipidemia (21.3%). Small vessel strokes were the most common, accounting for 48% of all the patients, followed by large vessels getting affected in 38.7% of the cases. Prevalence IDA was 24%. (95% confidence interval: 14.9%-35.3%). However, the proportion of IDA among patients with severe stroke was 84.6% compared to 11.3% in non-severe strokes (p=0.001).* ***Conclusion:*** *Prevalence of IDA in acute ischemic stroke is significant and it is associated with severe stroke in our hospital.*

Keywords: *Ischaemic stroke, iron deficiency anaemia.*

Introduction: A cerebrovascular accident (CVA), or stroke, is the rapid loss of brain function due to a disturbance in the blood supply to the brain. According to the latest report from the Centers for Disease Control and Prevention, mortality from stroke was the fourth leading cause of death in the United States in 2008. Stroke was a leading cause of severe long-term disability.[1] Nearly half of older stroke survivors were noted to experience moderate to severe disability.[2] Care for stroke survivors has been estimated to cost $18.8 billion in health care expenses within the United States during 2008, in addition to $15.5 billion as a result of lost productivity and premature mortality.[3] There are many established risk factors of stroke: hypertension, diabetes mellitus, dyslipidemia, etc.[4,5] However, the cause of stroke in about 30% of the cases remains undetermined, especially in young adults.[6]

Therefore there is a need to focus on discovering other risk factors. Anaemia is implicated as an important risk factor in the development of cerebrovascular and cardiovascular diseases. The focus was mainly on sickle cell anaemia and not on non-sickle anaemia. Anaemia is the most common blood disorder and proved to be highly related to cardiovascular diseases and cerebrovascular accidents.[7-11] Recently, iron deficiency anaemia (IDA) has been proposed as a stroke risk factor.[12,13] Iron deficiency decreases the amount of haemoglobin which in turn compromises the oxygen-carrying capacity of the blood. Anaemia is a hyperdynamic state which increases blood flow and

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turbulence leading to endothelial injury favoring thrombosis. Secondary reactive thrombocytosis in IDA also makes blood hypercoagulable.[14]

Bangladesh is a country where the stroke is the third leading cause of death. WHO ranked Bangladesh's mortality rate due to stroke as number 84 in the world. The reported prevalence of stroke in Bangladesh is 0.3%, although no data had been recorded.[15] In one study by ICDDRB found that most anaemia in rural Bangladesh was as high as 60%, but only half of the anaemic children were iron deficient.[16] IDA is an established risk factor for ischaemic stroke in children. Hence, if IDA can be established as a risk factor for stroke in adults, many major cerebrovascular events can be prevented. Therefore, IDA as a possible cause of stroke should be studied. Extensive literature search reveals to date, no such study was done. One case report had been reported as a probable cause of stroke due to IDA in 2008 by Boshak et al.[17] We aimed to investigate the prevalence of IDA in ischaemic stroke patients admitted to a tertiary hospital of Bangladesh.

Materials and methods:

A total of 75 subjects with first-ever stroke consecutively admitted to the Department of Neurology of Comilla Medical College Hospital was recruited for the study from February 2021 to May 2021. Inclusion criteria were age between 30 and 90 years and patients presenting with the first-ever stroke. Diagnosis of stroke was made based on findings from Neuroimaging (either of CT or MRI). Patients with intracerebral haemorrhage, subarachnoid and subdural haemorrhage, post trauma features, history of the previous stroke, previously diagnosed cases of sickle cell anaemia and other haemoglobinopathies were excluded from the study.

A structured questionnaire was used to collect information on demographic variables, stroke severity (with the help of the National Institute of Health Stroke Scale [NIHSS]), stroke subtype using TOAST criteria, vascular risk factors, and stroke workup. Patients were labeled as hypertensive if systolic blood pressure was greater than 140 mm Hg or/and diastolic blood pressure was greater than 90 mmHg during admission in the hospital or if the patient was on antihypertensive drugs at the time of entry. We classified the patient as diabetic if self-reported fasting glucose level was 120 mg/dL or more or if the patient was on hypoglycemic agents or insulin. Patients having serum high-density lipid of 100 mg/dL or less and/or serum low-density lipid of 100 mg/dL or more and/or fasting serum cholesterol of 200 mg/dL or more were labeled as having dyslipidemia. Smokers were the patients who had smoked ten or more cigarettes for ten or more years. Electrocardiogram was used to check for atrial fibrillation.

Complete blood count was done using Wheisman Auto Haematology Analyzer (Model - AC-310) ,Random blood sugar, S. Creatinine, Iron Profile [S. Iron, S. Ferritin, Total Iron Binding Capacity(TIBC)] were conducted using the methodology & reference range of department of clinical pathology Comilla Medical College Hospital. IDA was defined as serum ferritin level <20 µgm/L in males and <40 µgm/L in females.[18]

Patients or their next of kin were briefed about the purpose and nature of the study. Written consent was obtained from the patients or their next of kin in case of incapacitation of the patients. Ethical approval was obtained from the Ethical Review Committee of Comilla Medical College. Upon receiving the patients' consent or their nearest relative's consent, qualified medical personnel, not below senior medical officer and assistant register, examined and interviewed the patient or the patient's attendant about past medical and personal history and recorded the variable of interest.

Standardized Data Collection Form was used in recruiting patients. Data were managed using Statistical Package for Social Science (SPSS) for Windows Version 23. The presentation expressed data as mean ± SD and number (percent) as appropriate. Chi-squared tests were performed, where applicable, to calculate the statistical difference between corresponding groups and/or association between groups. ⊠ value <0.05 was taken as the level of significance.

Results:

The results are showed in table and graph Data were presented as frequency (percentage) if not mentioned otherwise.

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Table 1: Sociodemographic characteristics of the patients with acute ischemic stroke (n=75)

Variables		Frequency	Percentages
Age, years			
	Mean ±SD	65.8±11.4	
	Range	38-90	
	≤60 years	28	37.3
	>60 years	47	62.7
Sex			
	Male	45	60.0
	Female	30	40.0
Occupation			
	Housewife	45	60.0
	Business	12	16.0
	Service	9	12.0
	Others	9	12.0
Education			
	Illiterate	24	32.0
	Primary	27	36.0
	Secondary	20	26.7
	Graduate	4	5.3
Socioeconomic class			
	Lower	21	28.0
	Middle	54	72.0

The mean age of the stroke patients was 65.8 years, and most patients (60%) were male. Most patients (62.7%) were more than 60 years of age. Most patients were illiterate (32.0%) or had education up to the primary level (36.0%). Most of the patients (72.0%) were from the middle socioeconomic class.

Table 2: Risk factors of stroke patients with acute ischemic stroke (n=75)

Risk factors	Frequency	Percentages
Hypertension	55	73.3
Diabetes mellitus	37	49.3
Smoking	21	28.0
Ischemic heart disease	19	25.3
Dyslipidemia	16	21.3
History of stroke	7	9.3
Renal impairment	7	9.3
Valvular heart disease	2	2.7
Atrial fibrillation	2	2.7

Hypertension was the most prevalent risk factor present in 73.3% of the cases, followed by diabetes mellitus (49.3%), smoking (28.0%), ischaemic heart disease (25.3%), and dyslipidemia (21.3%).

Table 3: Risk factors of stroke among family members of the patients with acute ischemic stroke (n=75)

Risk factors	Frequency	Percentages
Family history of Diabetes mellitus	18	24.0
Family history of Hypertension	13	17.3
Family history of Ischemic heart disease	10	13.3
Family history of stroke	10	13.3

About one-third of the stroke patients had a family history of diabetes.

Table 4: Types of stroke of the patients with acute ischaemic stroke (n=75)

Stroke characteristics		Frequency	Percentages
Stroke type			
	Small vessel	36	48.0
	Large vessel	23	30.7
	Cardioembolic	4	5.3
	Unknown	12	16.0
Stroke severity			
	Severe stroke	13	17.3
	Nonsevere stroke	62	82.7

Small vessel strokes were the most common, accounting for 48.0% of all the patients, followed by large vessel stroke in 30.7% of the cases. Cardioembolic stroke was present in 5.3%, while the cause was unknown in 16.0% of the stroke cases. Thirteen patients (17.3%) had a severe stroke (NIHSS score greater than 14).

Table 5: Hemoglobin and iron profile of the patients with acute ischaemic stroke

Parameters	Level	Frequency	Percentage
Hemoglobin			
	Normal	39	52.0
	Below normal*	36	48.0
Serum iron			
	≥50 µgm/dl	45	60.0
	<50 µgm/dl	30	40.0
Serum ferritin			
	Normal	57	76.0
	Below normal**	18	24.0
Total iron binding capacity			
	≤355 µgm/dl	58	77.3
	>355µgm/dl	17	22.7

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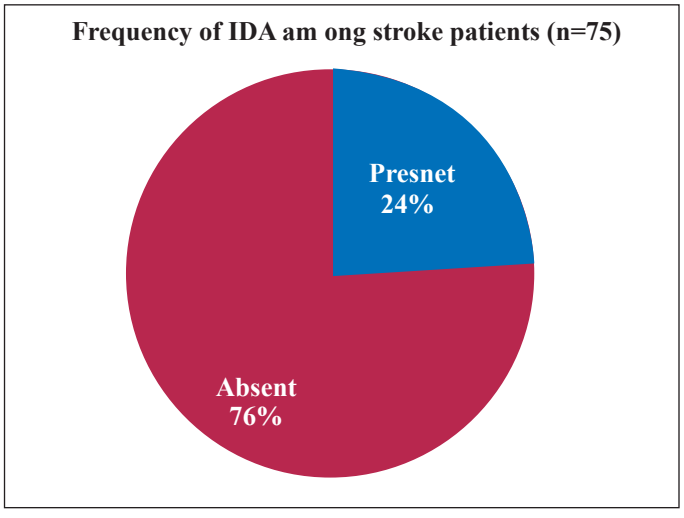
Anaemia statuses of the patients were determined by measuring hemoglobin and iron profile. About half of the patients were (48%) anaemic.
* <12 g/dl in women and <13 g/dl in men **<20 µgm/L in males and <40 µgm/L in females

Figure 1: Prevalence of IDA among patients with acute ischaemic stroke.



We identified that out of 75 patients with acute ischaemic stroke, 18 (24%.0; 95% confidence interval: 14.9%-35.3%).

Table 6: Association demographic factors and IDA in stroke patients

Variables		IDA absent	IDA present	P value*
Age				
	≤60 years	21 (75.0)	7 (25.0)	**0.876**
	>60 years	36 (76.6)	11 (23.4)	
Sex				
	Male	31 (68.9)	14 (31.1)	
	Female	26 (86.7)	4 (13.3)	
Economic class				
	Lower	18 (85.7)	3 (14.3)	**0.219**
	Middle	39 (72.2)	15 (27.8)	
Education				
	Illiterate	20 (83.3)	4 (16.7)	
	Primary	20 (74.1)	7 (25.9)	**0.784**
	Secondary	14 (70.0)	6 (30.0)	
	Graduate	3 (75.0)	1 (25.0)	

Iron Deficiency Anaemia was detected in a higher proportion among patients' ≤60 years, male patients, patients with middle socioeconomic class, and patients with secondary educational level compared to their counterparts. However, none of these differences was significant statistically.
Data were presented as frequency (percentage). *P values were obtained from the Chi-square test.

Table 7: Association between IDA and other risk factors of ischaemic stroke

Risk factors	IDA absent	IDA present	P value*
Hypertension	44 (80.0)	11 (20.0)	0.179
Diabetes mellitus	27 (73.0)	10 (27.0)	0.545
Smoking	18 (85.7)	3 (14.3)	0.219
Ischemic heart disease	12 (63.2)	7 (36.8)	0.129
Dyslipidemia	10 (62.5)	6 (37.5)	0.154
History of stroke	5 (71.4)	2 (28.6)	0.769
Renal impairment	7 (100.0)	0 (0)	0.118
Valvular heart disease	1 (50.0)	1 (50.0)	0.425
Atrial fibrillation	1 (50.0)	1 (50.0)	0.425

Traditional risk factors had no significant association with the presence of IDA.
Data were presented as frequency (percentage). *P values were obtained from the Chi-square test.

Table 8: Association IDA with stroke type and severity

Stroke characteristics		IDA absent	IDA present	P value*
Stroke type				
	Small vessel	20 (87.0)	3 (13.0)	
	Large vessel	25 (69.4)	11 (30.6)	0.499
	Cardioembolic	9 (75.0)	3 (25.0)	
	Unknown	3 (75.0)	1 (25.0)	
Stroke severity				
	Severe stroke	2 (15.4)	11 (84.6)	0.001
	Nonsevere stroke	55 (88.7)	7 (11.3)	

The proportion of patients with IDA was higher in patients with large vessel strokes (30.6%) than patients with small vessel stroke (13%), but the difference was not significant statistically. IDA was more common in patients with severe stroke at admission than those with non-severe stroke (84.6% versus 11.3%, p=0.001).
Data were presented as frequency (percentage). *P values were obtained from the Chi-square test.

Discussions:
Understanding the risk factors for ischemic stroke occurrence must be the priority for targeted preventive measures. Risk factors associated with ischemic stroke are age, male population, hypertension, diabetes mellitus, smoking and alcohol use. IDA has been suggested to be associated with stroke, but few cases have proven it thus far. In the present study, the prevalence of IDA among patients with acute ischaemic stroke was 24%. Anaemia is a

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common disease in about 10% of people age ≥ 65 years 7 its prevalence increase with age.19 Ischemic stroke is frequently accompanied by anaemia, previous studies have confirmed an average prevalence rate of 15-20%.[20-24] and a maximum prevalence of 30%.[25] IDA is the most typical type of anaemia, accounting for nearly half of all anaemia cases worldwide. Most of the patients with anaemia are asymptomatic, so that the actual incidence might be higher than reported. The incidence of IDA is very high in developing countries.[26]

In a study conducted by Chellan and his colleague, results showed that more than 95% of children, adolescent girls and pregnant women suffer from anaemia.[5] The association of stroke and IDA has been explained based on three physiological mechanisms: hypercoagulable state, thrombocytosis, and hypoxia.[12]

The possible reason for the IDA as a risk factor for stroke could be a decrease in haemoglobin level in the blood would compromise the oxygen-carrying ability of the blood flow resulting in low oxygen delivery to the brain, causing hypoxia and subsequently increase the risk of cerebrovascular or cardiovascular diseases. Another possible mechanism that may explain the association between IDA and stroke is secondary thrombocytosis. This mechanism is supported by findings of the association of thrombotic and embolic ischemic stroke with IDA. Cases of carotid thrombus associated with IDA and thrombocytosis have been reported in adults.[27-29] Anaemic patients need more blood to flow to the brain to compensate for the lack of oxygen. Therefore increase in blood flow can cause endothelial damage, causing a cascade of thrombus formation.[6] In the study done by Dubyk et al., they supported the role of IDA as a risk factor for stroke in elderly patients.[14]

In our study of 75 patients with stroke, 24% were anaemic due to IDA. This study thus suggested an association between IDA and ischemic stroke. However, there are various associated comorbid conditions with stroke. A study conducted by Ellie Choi et al. showed that blood transfusion might be considered adjuvant therapy in treating stroke patients.[28] In the case presented by Mehta et al., the ischemic stroke patient showed marked improvement after receiving a blood transfusion.[12]

The mean age of the stroke patients, around sixty-five years, is consistent with previous findings from a stroke registry study in Bangladesh.[30] Most of the patients from a stroke registry in the USA presented with stroke at 71 years.[31] The lower percentage of female stroke patients being registered implies either a low prevalence of stroke among females or lower access of female stroke patients to the tertiary care hospital.

In this sample, atherosclerosis in the small vessel was responsible for most of the stroke cases. The majority of these patients had dyslipidemia. Hypertension and diabetes were other risk factors that were present in them. Dyslipidemia, hypertension, and diabetes are important risk factors for stroke, as reported previously.[30,32] Proportion of two important risk factors, diabetes and hypertension, are more common among stroke patients in Bangladesh, as revealed in a previous study.[30]

Understanding social and demographic characteristics in stroke patients is important to understand the population at risk and address the risk factors. The present study aims to present the sociodemographic picture of patients with ischemic stroke in a developing country like Bangladesh. The study shows higher incidences of stroke in males than females, with most cases in the age group more than 60 years. Hypertension was found to be the commonest risk factor. Understanding these variables will help to formulate preventive action plans for specific risk factors and targeted population groups.

Limitations: This study has several limitations. First, the sample size was small. All the patients were selected from a public tertiary hospital conveniently. Data on the nutrition practices of the patients were not available, and we were not able to explore causal mechanisms for the development of IDA. Finally, the study's cross-sectional design was not appropriate to define a causal relationship between two variables.

Conclusions: From the present study, it can be concluded that IDA is common in patients with acute ischaemic stroke, and there is significant association between the severity of the ischemic stroke and IDA.

Conflict of interest: There is no conflict of interest.

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Recommendations: Early detection of anaemia will help to decrease the incidence of stroke cases. Patients found to have IDA should be more aggressively screened and managed for the possible underlying bleeding source and /or iron deficiency status, to reduce the risk of subsequent ischemic stroke. While a thorough neurologic evaluation is not often considered in patients presenting with signs and symptoms of severe anaemia, vigilance regarding focal neurologic deficits should prompt suspicion for ischemic stroke in patients with significantly low hemoglobin levels. However, more studies should be conducted with a larger sample size from different centers in a case-control design to establish a definite relationship between ischemic stroke and IDA.

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