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# Association of Serum Vitamin B12 level and Acute Ischaemic Stroke

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## Abstract

***Background:*** *Stroke, the second leading cause of death worldwide is a multifactorial disease. Several risk factors had been identified for stroke. Hyperhomocysteinemia is one of the latest additions among the risk factors responsible for ischaemic stroke. Though vitamin B12 is one of the causative factors of hyperhomocyteinemia, very few studies showed a relation between ischaemic stroke and Vitamin B12 deficiency. So, this study aimed to find out the association between vitamin B12 deficiency and acute ischaemic stroke.* ***Methods****: This case-control study was conducted at the department of Neurology, Mymensingh Medical College & Hospital. Fifty patients of first ever acute ischemic stroke and 50 apparently healthy controls, matched for age (56.90±9.88 versus 52.88±6.18) and sex (31 male and 19 female) were recruited. Vitamin B12 was measured by Enzyme-linked immunosorbent assay and its status was considered as low, borderline and normal with vitamin B12 levels of <180, 180-200 and 200-800 pg/ml, respectively.* ***Results:*** *Mean (±SD) concentration of vitamin B12 in stroke cases and control were 223.84 (±71.764) pg/ml and 306 (±115.40) pg/ml respectively (p=<0.001). Low and borderline vitamin B12 was observed in 22% and 58%of ischaemic stroke patients and 12% and 30%of the healthy controls. Participants with borderline Vitamin B12 plasma level had significantly higher odds of being in the cases compared to participants with normal vitamin B 12 plasma level (OR: 5.61; 95% CI:2.16-14.52, p=<0.001). Similarly participants with low plasma level of vitamin B12 were 5.32 times more likely to be in ischaemic stroke group compared to participants with normal plasma vitamin B12 level (OR: 5.32; 95% CI:1.56-18.14, p=0.008).* ***Conclusion:*** *The study concluded that low serum vitamin B12 level was associated with acute ischaemic stroke.*

***Key words:*** *Vitamin B12, Acute Ischemic Stroke, Hyperhomocysteinemia*

## Introduction:

Stroke is a sudden onset of focal neurological deficit, a major cause of morbidity and mortality and the second leading cause of death worldwide[1,2]. Stroke has a heterogeneous etiology, caused by modifiable (high blood pressure,

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cigarette smoking, diabetes, high blood cholesterol levels, heavy alcohol drinking, obesity) and non-modifiable (age, sex and family history) risk factors[3]. New potentially treatable factors contributing to stroke risk are emerging continuously[4].

Hyperhomocysteinemia is one of the established risk factors for ischaemic stroke. Homocysteine is a highly reactive amino acid and is toxic to vascular endothelium, potentiates auto-oxidation of low density lipoprotein, and promotes both arterial and venous thrombosis. Vitamin B12 deficiency results in the accumulation of homocysteine in blood. Hence, these patients with hyperhomocysteinemia secondary to vitamin B12 deficiency are at high risk for cerebrovascular disease[5, 6].

Decreasing intestinal absorption with aging, being vegetarian and genetic polymorphisms may contribute to the deficiency of vitamin B12 and 10-40% of general population is found deficient of Vitamin B12. This may contribute to increase number of stroke[7]. Patient with recurrent stroke was found to have low B12 and a high homocysteine level and improved markedly with vitamin B12 supplementation[8]. A few recent studies pointed out the association between vitamin B12 level and ischemic stroke[6-10].

However, though stroke is a growing problem in Bangladesh[11,12], the issue of vitamin B12 as a moldable risk factor gained less attention in the research till date[13]. Contemplating this background, this study was planned to assess the association between vitamin B12 and ischaemic stroke in a group of Bangladeshi population. By measuring serum Vitamin B12 level of a stroke patient, if any variation of its normal limit correlates with ischaemic stroke then this study might give an idea how ischaemic stroke can be prevented.

**Materials and methods:**

This case-controlstudy was performed in Mymensingh Medical College Hospital, Mymensingh, Bangladesh. Fifty admitted patients in Neurology and Medicine department of this hospital who had a diagnosis of acute ischaemic stroke (within 7 days of symptom onset) fulfilling the WHO Stroke criteria and evident by neuroimaging study were in included in the study. Patient of haemorrhagic stroke or TIA or previous ischaemic stroke, patients with a diagnosed of megaloblastic anaemia, chronic kidney disease or gastrointestinal disease, those taking vitamin B12, Folic acid supplements within last 3 months and strict vegetarian person were excluded. Another fifty age and sex matched apparently healthy individuals importantly with no prior history of stroke or transient ischaemic attacks were taken as control.

The data of the participants were collected by a predesigned case record form containing a questionnaire regarding age, sex, residential location, monthly family income, and risk factors for stroke (hypertension, diabetes, ischemic heart disease, alcoholism and smoking) and a checklist to note the vitamin B12 and lipid profile levels. Hypertension and diabetes was diagnosed as having a previous diagnosis of these conditions by a registered physician or patients on anti-hypertensive or anti diabetic medications. Smoking was defined ever or never smokers.

Following interviewing the subjects of both patients with acute ischaemic stroke group and apparently healthy respondents group, blood samples of about 5.0 ml were collected from them by venepuncture under all aseptic precautions for estimation of lipid profile and vitamin B12. For vitamin B12 level estimation; 3 ml serum was taken from a serum seperating tube, the sample was frozen and analysed by Enzyme-linked immunosorbent assay. Serum vitamin B12 Level <180, 180-200, 200-800 and >800 pg/ml were respectively considered as low, borderline, normal and high level[14].

Quantitative variables were expressed as either mean ± standard deviation (SD) or median (interquartile range) and qualitative variables were presented as percentages or proportions. Student's t-test or Mann Whitney U test was used to analyze quantitative variables while qualitative variables were compared by means of Chi-square test between two groups. Logistic regression analysis was done to determine the odds ratio (with 95% confidence interval). $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 23.0.

Informed consent was obtained from competent patients before enrollment. In patients who were

unable to give fully informed consent, assent was obtained from legal relatives. The study protocol was approved by the Ethical Review Committee of Mymensingh Medical College (Memo number: MMC/IRB/2019/113 Date: January 28, 2019).

**Results:**

Mean age of the stroke patients was 56.40 (±9.80) years with a male predominance (64%). Both the stroke cases and healthy control groups were similar in terms of the distribution of age, sex and residential location. However, monthly family income was significantly lower in stroke patients compared to healthy controls (p=0.008) (Table I).

In respect of the risk factors, hypertension, diabetes mellitus, Ischaemic Heart Disease, and smoking displayed significantly higher rates of prevalence in the patient population compared to apparently healthy respondents. However, habit of alcohol drinking was also show the same trend but without any statistical significance. Mean concentration of TG, TC and LDL were significantly higher in stroke patients compare to apparently healthy respondents and HDL was significantly lower among stroke patient than healthy respondents (Table II).

Vitamin B12 level in the studied population are summarized in Table III. It depicts that, mean and median vitamin B12 levels were significantly lower among ischaemic stroke cases compare to apparently healthy controls ($p<0.05$).

Table IV shows odds ratios of ischaemic stroke by vitamin B12 status. Participants with borderline Vitamin B12 plasma level had significantly higher odds of being in the cases compared to participants with normal vitamin B 12 plasma level (OR: 5.61; 95% CI:2.16-14.52). Similarly participants with low plasma level of vitamin B12 were 5.32 times more likely to be in ischaemic stroke group compared to participants with normal plasma vitamin B12 level (OR: 5.32; 95% CI:1.56-18.14).

Relation of vitamin B12 level with other variables in the cases of ischaemic stroke was investigated in the study. Table 5 depicts that, there was no significant difference in the mean vitamin B12 concentration in male or female patients, patients with or without hypertension, diabetes, smoking history and ischaemic heart disease.

**Table-I**

*Socio-demographic characteristics of the participants stratified by acute ischaemic stroke patients and apparently healthy control*

| Characteristics | Ischaemic stroke patients (n=50) | Healthy Controls (n=50) | p value |
|---|---|---|---|
| Age (years) | | | |
| ≤40 | 1 (2.0) | 1 (2.0) | |
| 41-50 | 18 (36.0) | 20 (40.0) | 0.920† |
| 51-60 | 17 (34.0) | 18 (36.0) | |
| >60 | 14 (28.0) | 11 (22.0) | |
| Mean ± SD | 56.40±9.80 | 54.10±6.76 | 0.175* |
| Sex | | | |
| Male | 32 (64.00) | 31 (62.00) | 0.836† |
| Female | 18 (36.00) | 19 (38.00) | |
| Residence | | | |
| Rural | 32 (64.00) | 35 (70.00) | 0.534† |
| Urban | 18 (36.00) | 15 (30.00) | |
| Monthly family income | | | |
| Median (IQR) (BDT) | 20,000 (16,000 - 30,000) | 27,000 (20,000-35,000) | 0.008** |

Data were expressed as frequency (percentage) if not otherwise mentioned. *p values were obtained from unpaired Student t test, †Chi-square test, **Mann Whitney U test.BDT: Bangladeshi taka; IQR: Interquartile range.

**Table-II**

*Distribution of risk factors of stroke in the participants stratified by acute ischaemic stroke patients and apparently healthy respondents*

| Risk factors | Ischaemic stroke patients (n=50) | Healthy Controls (n=50) | p value |
|---|---|---|---|
| History of smoking | 22 (44.0) | 8 (16.0) | 0.002† |
| History of Alcohol intake | 0 (0) | 0 (0) | NA |
| Hypertension | 25 (50.0) | 3 (6.0) | <0.001† |
| Diabetes mellitus | 20 (40.0) | 2 (4.0) | <0.001† |
| Ischaemic heart diseases | 17 (34.0) | 0 (0) | <0.001† |
| LDL (mg/dl) | 97.5±8.3 | 85.4±20.6 | <0.001* |
| HDL (mg/dl) | 35.9±5.9 | 39.1±6.1 | 0.008* |
| TG (mg/dl) | 152.6±27.7 | 143.4±12.9 | 0.037* |
| TC (mg/dl) | 197.2±23.1 | 172.7±23.1 | <0.001* |

Data were expressed either as frequency (percentage) or mean ± SD as appropriate. †p values were obtained from Chi-square test; *p values were obtained from Student t test. LDL: Low density lipoprotein, HDL: High density lipoprotein; TG: Triglyceride; TC: Total cholesterol; NA: Not Applicable.

**Table-III**

*Comparison of vitamin B 12 level between case and control*

| Vitamin B12 level(pg/ml) | Ischaemic stroke patients (n=50) | Healthy Controls (n=50) | P value† |
|---|---|---|---|
| Mean ± SD | 209.1±59.9 | 309.6±116.6 | |
| Median (IQR) | 190.0 (181.0-196.0) | 320.0 (190.0-410.0) | <0.001 |
| Range | 160.0-410.0 | 164.0-510.0 | |

†P value was obtained from Mann-Whitney U test.

**Table-IV**

*Vitamin B12 status of the studied population stratified by case and control*

| Vitamin B12 status (Vitamin B12 level) | Ischaemic stroke patients (n=50) | Healthy Controls (n=50) | Crude Odds ratio (95% CI for OR) | P value‡ |
|---|---|---|---|---|
| Normal (201-800 pg/ml) | 10 (20.0) | 29 (58.0) | Reference category | NA |
| Borderline(180-200 pg/ml) | 29 (58.0) | 15 (30.0) | 5.61(2.16-14.52) | <0.001 |
| Low (<180 pg/ml) | 11 (22.0) | 6 (12.0) | 5.32(1.56-18.14) | 0.008 |

‡P values were obtained from logistic regression analysis. OR: Odds ratio; CI: Confidence interval; NA: Not applicable.

**Table-V**

*Relationship between vitamin B12 level and other variables in case (n=50)*

| Variables | Serum vitamin B 12 (pg/ml) | | p value† |
|---|---|---|---|
| | Mean ± SD | Mean difference | |
| Age | | | |
| ≤50 years (n=19) | 224.95±75.73 | 25.53 | 0.145 |
| > 50 years (n=31) | 199.41±46.51 | | |
| Sex | | | |
| Male (n=32) | 202.19±42.25 | 19.56 | 0.280 |
| Female (n=18) | 221.44±75.29 | | |
| Hypertension | | | |
| Present (n=25) | 204.52±56.51 | 9.2 | 0.0592 |
| Absent (n=25) | 213.72±63.94 | | |
| Diabetes Mellitus | | | |
| Present (n=20) | 205.00±61.49 | 6.86 | 0.697 |
| Absent (n=32) | 211.87±59.72 | | |
| IHD | | | |
| Present (n=17) | 190.76±32.90 | 27.81 | 0.121 |
| Absent (n=33) | 218.57±68.42 | | |
| Smoking | | | |
| Present (n=22) | 190.86±32.49 | 32.60 | 0.55 |
| Absent (n=28) | 223.45±72.15 | | |

*p values were obtained from unpaired Student's t test.

**Discussion**

The current study was aimed to determine the relation between the plasma vitamin B12 level and acute ischaemic stroke in a group of Bangladeshi patients. Our hypothesis was vitamin B12 level is lower in patients with acute stroke compared to the age and sex matched apparently healthy respondents without any previous history of stroke. Finally, the study revealed a significant association between vitamin B12 and ischaemic stroke. Mean vitamin B12 concentration was significantly lower in stroke patients compare to apparently healthy respondents and prevalence of low vitamin B12 was also higher in stroke patients compared to apparently healthy respondents. Studies till date investigating the associations between vitamin B12 plasma levels and the risk of stroke are proving inconsistent results[13,15-17].

Mean age of the stroke patients were 56.90±9.88 years and apparently healthy respondents were 56.40±9.80years, with no significant difference between two groups. In previous same type of study to explore the association of vitamin B12 with ischaemic stroke the mean age was 54.7±14.7 years[15], and in other study it was 40.71 ± 9.46 years[16]. Male to female ratio in the present study was 1.78:1 and this male predominance in the stroke patients was also in agreement with the previous studies[13-16].

Diabetes mellitus, hypertension and ischaemic heart disease, family history of hypertension and diabetes mellitus, smoking are considered as significant risk factors of stroke[3]. In the present study hypertension, diabetes mellitus, ischemic heart disease, and smoking displayed significantly higher rates of prevalence in the patient population compared to healthy respondents. Regarding dyslipidemia, mean concentration of TG, TC and LDL were significantly higher in stroke patients compare to apparently healthy respondents and HDL was significantly lower among patients population than apparently healthy respondents. These risk factors distributions of the present study were also more or less in agreement with other studies conducted in and around our country[15-19].

The present study demonstrated significant differences in the mean concentration of serum

vitamin B12 between stroke patients and apparently healthy respondents [209.1 (±59.9) pg/ml versus 309.6 (±116.6)pg/ml, p<0.001]. Another study from Bangladesh conducted almost a decade ago reported similar results, where the mean concentration of serum vitamin B12 was 231.02±10.81 and 278.72±15.88pg/ml respectively (p<0.001)[13]. Study conducted in Indian population reported mean value of 282.46±161.52 and 480.42±248.92 pg/ml respectively in stroke patients and controls[16].Kocer et al. from Turkey also observed a significantly lower vitamin B12 level among patients with stroke compared to control (245.50±72.9 pg/ml vs 343.2±113 pg/ml, p=<0.001)[17]. However, contrasting evidences were also available in the literatures. Like, Maheshwari et al. from India and Omrani et al. from Iran observed no significant differences in the mean vitamin B12 level between ischaemic stroke and control subjects[15, 18].

The present study also demonstrated a significant association of vitamin B12 level and stroke, where majority of patients with stroke were found to have borderline level of vitamin B12 (52%), and 22% of patients had a deficient level. Only 20% of them had a normal level of vitamin B12. While in the apparently healthy respondents group, 58% have a normal level of vitamin B12 level, and only 12% had a deficiency of vitamin B12 level and 30% had borderline level of vitamin B12. In contrast, Maheshwari et al. reported that, though prevalence of low vitamin B12 level was higher in stroke patients compared to healthy controls it was not statistically significant (41.7% versus 30%, p=0.237)[15].

Kumawat et al. concluded that hyper-homocysteinemia was a significant risk factor for ischaemic stroke in their study populations group and vitamin B12 deficiency had a major role to play in its causation[16]. Casas et al. observed and described a causal link between hyperhomocysteinemia and stroke[20]. Vitamin B12 deficiency leads to impairment of methionine synthase, a vitamin dependent enzyme, resulting in the accumulation of homocysteine and trapping folate as methyl-tetrahydrofolate[21]. The present study and other previous studies supported this possible role of deficient Vitamin B12 in the causation of ischaemic stroke[13,16,17,22].

**Limitations:**
Due to cross-sectional design of the study, it was not possible to make comment about the causation. Small sample size, purposive sampling technique and sample from a single government level tertiary care hospital were some of the other limitations of the present study. Finally, confounding variables were not eliminated and apparently healthy respondents were chosen from the same source of cases.

**Conclusion:**
In conclusion, this study showed that serum vitamin B12 level is significantly lower in acute ischaemic stroke patient group than apparently healthy population group. Therefore, vitamin B12 deficiency should be considered as a risk factor of acute ischaemic stroke and early detection of serum vitamin B12 level deficiency may play an important role in prevention of acute ischaemic stroke.

**Recommendations:**
Low serum vitamin B12 level could be considered as a risk factor for acute ischaemic stroke. So, assessment and correction of serum Vitamin B12 level among persons vulnerable to stroke can be added to the preventive strategy of ischaemic stroke. However, further prospective multi-center study with larger sample size should be conducted.

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**Conflict of Interests:** The authors declare no conflict of interest in this study.

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