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ORIGINAL ARTICLES

Relationship Between Homocysteine and Carotid Artery Stenosis in Ischemic Stroke

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Abstract:

Background: *Epidemiologic studies have identified hyper-homocysteinemia as a possible risk factor for atherosclerosis. The aim of my study was based on evaluation of relationship between homocysteinemia with carotid artery stenosis in ischemic stroke patients.* ***Methods and materials:*** *It was a prospective observational study conducted in the Department of Neurology, Sir Salimullah Medical College & Mitford hospital, Dhaka. Thirty six consecutive patients with ischemic stroke were analyzed by serum total homocysteine, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride and extracranial Doppler ultrasonography and vascular risk factors were recorded. Equal number of controls of same ages were compared with the case group.* ***Result:*** *Mean fasting blood sugar, serum fasting total cholesterol (TC), serum fasting Low density lipoprotein (LDL) were significantly higher in case group (p=0.001). Serum TC and LDL had a positive correlation with serum homocystine (p=0.001). Serum High density lipoprotein (HDL) had a negative correlation (p=0.718) and serum triglyceride (TG) had a negative correlation (p = 0.182). Total plasma fasting homocysteine level in case group was 21.89 ± 9.38 ìmol/l and control group was 12.31 ± 3.27 ìmol/l, (p=0.001). Elevated fasting homocysteine level was found in 75.0% of the ischemic stroke patients and in 16.67% of healthy controls (p=0.001).On the basis of clinical evaluation and results of imaging studies, etiological classification of the ischemic stroke patients were made, where 36.1% cases were small artery disease, 38.9% large artery disease, 8.3% cases cardioembolic and in 16.7 % other causes. Among the cases, carotid duplex study was found normal in seven cases (19.4%), Group 1 findings in seven cases (19.4%), group 2 findings in eight cases (22.2%), group 3 findings in thirteen cases (36.1%) and group 4 findings in one case (2.8%). All abnormal carotid duplex findings were significantly higher among cases with elevated level of homocysteine (p=0.001, 0.001, 0.001) .* ***Conclusion:*** *The incidence of hyperhomo-cysteinemia is higher in ischaemic stroke cases than that in age-sex matched healthy controls. Hyperhomocysteinemia in ischaemic stroke patients has been determined as vascular risk factor in our study. Significant correlation has been found between homocysteine concentration and intraluminal thickness and carotid artery stenosis.*

Key words: *Homocysteine, carotid artery stenosis, ischaemic stroke*

Introduction:

Hyperhomocysteinemia has been associated with premature peripheral vascular, cerebrovascular, and coronary artery disease. Hyperhomo-cysteinemia, has been identified as being associated with vascular disease, including cerebrovascular disease in

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general, particularly in subjects with significant carotid stenosis [1, 2]. Many case-control and cohort studies have identified a strong, independent and dose-related association between moderately elevated homocysteine and atherosclerotic vascular disease, including stroke[3, 4, 5].

In this study, we undertook a prospective case-control study of consecutive patients hospitalized with a first-ever ischemic stroke and examined specifically whether there may be an association between homocysteine, serum lipid profile, the degree of stenosis of carotid arteries and the specific etiologic subtypes of ischemic stroke. The current study was aimed to explore the relationship of serum homocysteine with carotid stenosis in ischemic stroke.

Methods:

This prospective, case-control study of serum total homocysteine as a potential risk factor for acute ischemic stroke. 36 consecutive male and female patients admitted in the department of Medicine and Neurology of Sir Salimullah Medical College & Mitford Hospital (Dhaka, Bangladesh) from January 2008 - June 2009 with the diagnosis of acute ischemic stroke was included in this study and they were compared with 36 control age-matched volunteer subjects of outpatient department. Criteria for entry into the study were as follows: (1) with neurological examination and neuroimaging (CT/MRI) methods, diagnosis of ischemic stroke was strictly verified within 48 hours, (2) no disorders related to hepatic, renal and endocrinologic functions, (3) no systemic malignancy, (4) The subjects that do not use any preparations including vitamin B12 and folic acid or any medications having antimetabolite effects such as methotrexate or phenytoin, etc.

Stroke was defined as a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs focal and at times global loss of brain function, with symptoms lasting >24 hours or leading to earlier death, and with no apparent cause other than that of vascular origin [6].

On the basis of clinical evaluation and results of imaging studies, the neurologist classified all strokes into 4 major etiologic subtypes according to the following criteria[7].

1. Large-artery disease (LAD): ischemic stroke with
   (a) evidence of extracranial or intracranial occlusive large-artery disease and
   (b) no cardioembolic source, and
   (c) clinical opinion that the most likely cause of brain infarction was atherothrombosis involving the aortic arch, carotid arteries or major branches, or vertebral, basilar, and posterior cerebral arteries;
2. Small-artery disease (SAD, lacunar): ischemic stroke with
   (a) Consciousness and higher cerebral function maintained plus
   (b) One of the classic lacunar syndromes or nonlacunar small-artery syndromes and
   (c) CT or MRI brain scan, performed within 3 weeks of symptom onset that is either normal or shows a small deep infarct in the basal ganglia, internal capsule, or brain stem;
3. Cardioembolic (CE) disease: ischemic stroke with
   (a) A major cardioembolic source plus
   (b) No definite evidence of occlusive large-artery disease, and
   (c) Clinical opinion that the most likely cause of brain infarction was embolism from the heart;
4. Other causes: ischemic stroke that did not meet criteria for one of the categories outlined above or where there was more than one likely explanation. All patients were examined by a neurologist and they had Cranial Tomography (CT) or Magnetic Resonance Imaging (MRI), Electrocardiography, Echocardiography, and high resolution B-mode Doppler Ultrasonography (DUSG) (made by a radiologist blinded to results of homocysteine levels). Clinical information including age, sex, history or current evidence of Hypertension (HT) [systolic blood pressure (SBP) >150mmHg and diastolic BP >90mmHg],

Diabetes Mellitus (DM) and cardiac disease, were recorded for all subjects. In case, venous blood samples were obtained after their admission and control subjects were both admission and outpatient department in the morning after an overnight fast of at least 12 hours into EDTA tubes. Serum total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), VLDL cholesterol (VLDL-C) and triglycerides were measured by using standard enzymatic procedures. Borderline for normal values were total cholesterol < 5.2 mmol/L, HDL-C > 1.0 mmol/L, LDL-C < 3.0 mmol/L, VLDL < 1.1 mmol/L and triglyceride < 2.3 mmol/L. Total plasma homocysteine level was measured in subjects within the first 48 hours after stroke onset. Plasma homocysteine levels were determined with FPIA (fluorescence polarization immunoassay) on the Abbott AxSYM system. Kit supplied from AxSYM Germany. The upper limit of the manufacturer and the laboratory was 15 µmol/L. Values above 15 µmol/L were acceptably high. Extracranial vessels were examined with the use of high resolution DUSG in a non-invasive manner. Real time scanner equipped with a 7.5 MHz imaging transducer. DUSG was done by ultrasonix, model-sonix SP from Germany. DUSG was done in Nuclear Medicine and Ultrasound, Mitford, Dhaka, Bangladesh.

The degree of stenosis of carotid arteries was recorded by the following criteria;

0. Normal,
1. Atherosclerotic lesions on one side <20% stenosis or nonstenotic plaque (Group 1),
2. 20-50% stenosis on one side or atherosclerotic lesions on both sides (Group2);
3. 50-70% stenosis on one side or 20-50 % stenosis on both sides (Group3);
4. Stenosis >70% on one side or 50-70 % on both sides and occlusion of one carotid artery on one side (Group 4).

Intima-Media Thickness (IMT) was defined as the distance between the characteristic echoes from the lumen intima and media-adventitia interfaces. Vertebral artery flow volume and mean systolic flow velocity were determined by using B-mode Doppler ultrasonography. The vertebral artery flow volume less than 200 ml/min were evaluated as vertebrobasilar insufficiency (VBI). Statistical analyses related with this study were performed by use of SPSS 9.0 package program. In the course of the evaluation of the data gathered, descriptive statistical methods (average, standard deviation) were used; in addition to these methods, free t test was used for the comparison between the paired groups through the use of the non-parametric tests taking into consideration the number of patients in the groups composed with the classification of the patient group by etiologies. The comparisons between the groups were evaluated with the chi-square test was used for the comparisons between the qualitative data. Correlations between numeric variables, like cholesterol, triglyceride and homocysteine were investigated by t test. The results of these tests were considered at the significance level of $p<0.05$ and the confidence interval 95%.

Results and observations

36 patients with ischemic stroke (18 female and 18 male) and 36 control subjects (18 male and 18 female) were included in the study. The mean age of the patient group was within the range of 50.28 ± 14.29 and the mean age of the control group was within the range of 51.08 ± 14.50 (TableI-I)

Table I

Distribution of age by group

Age (in year)	Group		p value*
	Case	Control	
<30	3 (8.3) #	4 (11.1)	
31-50	17 (47.2)	15 (41.7)	
51-70	14 (38.9)	15 (41.7)	
>70	2 (5.6)	2 (5.6)	
Total	36 (100.0)	36 (100.0)	
Mean ± SD	50.28 ± 14.29	51.08 ± 14.50	0.813

*t test was done to measure the level of significance.
#Figure within parentheses indicates in percentage.

In respect of the risk factors, HT, Ischemic Heart Disease (IHD), DM displayed significantly higher

rates of prevalence in the patient population. In the patient group, only HT was found to be significantly higher in CE group in respect of the distribution of the risk factors in the etiological subgroups (p=0.0.230); any significant difference has not been determined (Table II).

Table-II

Distribution of history of risk factors by group

Risk factors	Group		p value*
	Case	Control	
Hypertension(HT)	17 (47.2) #	12 (33.3)	0.230
Ischemic heart disease(IHD)	7 (19.4) #	6 (16.7)	0.759
Valvular heart disease	2 (5.6) #	0 (0.0)	0.151
Diabetes mellitus(DM)	9 (25.7) #	8 (22.9)	0.780

*Chi square test was done to measure the level of significance.
#Figure within parentheses indicates in percentage.

Mean, standard deviation of fasting total cholesterol, triglyceride, HDL-C, LDL-C and VLDL-C in patients and control group summarized in Table III. There was no statistical difference between the two groups.

Table III

Fasting blood sugar, serum fasting lipid profile and fasting total plasma homocysteine level by group

Parameter	Group		p value*
	Case(n=36)	Control(n=36)	
Fasting blood sugar (mmol/l)	8.30 ± 3.82	5.87 ± 1.77	0.001
Total Cholesterol (TC) (mg/dl)	207.14 ± 56.52	166.69 ± 28.55	0.001
HDL (mg/dl)	35.94 ± 15.95	39.14 ± 18.27	0.432
LDL (mg/dl)	137.06 ± 57.21	93.13 ± 26.44	0.001
Triglyceride (TG) (mg/dl)	205.19 ± 77.03	183.19 ± 60.60	0.182
Total plasma homocysteine level(fasting) (ìmol/l)	21.89 ± 9.38	12.31 ± 3.27	0.001

*t test was done to measure the level of significance.
#Figure within parentheses indicates in percentage.

In respect of the distribution of the patient group by etiology, the rates were determined as 38.9% for LAD, 36.1% for SAD, 8.3% for CE and 16.7% for Others (Table IV).

Table IV

Distribution of etiological subgroups in case group

Etiological subgroups	Frequency	Percent
Small artery disease(SAD)	13	36.1
Large artery disease(LAD)	14	38.9
Cardioembolic(CE)	3	8.3
Others	6	16.7
Total	36	100.0

#Figure within parentheses indicates in percentage.

Compared to the control subjects, the mean fasting plasma homocysteine level was found to be significantly higher (p<0, 01). While the homocysteine concentration was found within the normal levels in 25% of the patients, it was found to be elevated in 75% cases. The homocysteine level in the control group was found to be within normal levels for 83.33% of the control subjects; and only 16.67% of the control subjects displayed elevated levels of homocysteine. (Table V)

Table-V

Distribution of respondents according to level of homocysteine by group

Homocysteine	Group		Total	p value*
	Case (%)	Control (%)		
Normal	9(25.0) #	30 (83.33)	46 (63.89)	0.0.001
Elevated	27 (75.0)	6 (16.67)	26 (36.11)	
Total	36 (100.0)	36 (100.0)	72(100.00)	

*Chi square test was done to measure the level of significance.
#Figure within parentheses indicates in percentage.

In the determination of correlation between the homocysteine level and lipid levels in the patient group Serum TC and LDL had a positive correlation with serum homocystine with a p value 0.001. Serum HDL had a negative correlation with p value 0.718 and TG had a positive with a p value 0.205. (Table VI).

Table VI

Correlation between serum fasting lipid profiles with total plasma homocysteine level

Serum fasting lipid profiles	r value	p value
TC(mg/dl)	0.388	0.001
HDL(mg/dl)	-0.043	0.718
LDL(mg/dl)	0.416	0.001
TG(mg/dl)	0.151	0.205

Pearson's correlation was done to find the significance value.
Pearson's correlation, r = 0.151, p = 0.205

Evaluation of the Doppler parameters in the patients is shown in Table IV. IMT was found in 29 (80.4%) patients. There were 7 (19.4%) patients in the Group 1, 8 (22.2%) patients in the Group 2, 13 (36.1%) patients in the Group 3,1 (2.8%) patients in the Group 4 .(Table VII)

A higher tHcy level was found to be associated with plaque score independently. Family history of hypertension & DM. fasting blood sugar, serum fasting TC& LDL which were atherosclerotic risk factors.(Table VIII)

Significant correlation (p-0.001) has been determined between IMT and first 3 groups (1, 2, 3) in the patients that displayed elevated levels of homocysteine. (Table IX)

Table-VII

Distribution of carotid duplex by groups

Carotid duplex	Group		p value*
	Case	Control	
Normal	7 (19.4)#	27 (75.0)	0.001
Group 1	7 (19.4)	6 (16.7)	
Group 2	8 (22.2)	0 (.0)	
Group 3	13 (36.1)	2 (5.6)	
Group 4	1 (2.8)	1 (2.8)	
Total	36 (100.0)	36 (100.0)	

*Chi square test was done to measure the level of significance.
#Figure within parentheses indicates in percentage.

Table-VIII

Binary logistic regression analysis

					95.0% C.I. for EXP(B)	
Risk factors	B	Wald	p value	Exp(B)	Lower	Upper
Family history of hypertension	2.191	4.261	0.039	8.943	1.117	71.610
Family history of diabetes mellitus	-2.463	2.022	0.155	0.085	0.003	2.539
Fasting blood sugar	0.263	3.078	0.079	1.300	0.970	1.744
Serum fasting lipid profile TC	-0.011	.283	0.594	0.989	0.949	1.030
Serum fasting lipid profile LDL	0.035	1.977	0.160	1.035	0.986	1.087
Fasting total plasma homocysteine level	0.220	6.085	0.014	1.246	1.046	1.485

Table-IX

Correlation between homocysteine level and subgroups with Doppler study

Doppler findings	Normal homocysteine (n=9)	Elevated homocysteine (n=27)	p value
Normal	5	2	0.056
Group 1	1	6	0.001
Group 2	1	7	0.001
Group 3	2	11	0.001
Group 4	-	1	-
Total (%)	9	27	

*Chi square test was done to measure the level of significance.
#Figure within parentheses indicates in percentage.

Discussion:

In this study, we have aimed to determine the correlation between the plasma homocysteine level and stroke and to discover the association between the elevated plasma levels and the lipid levels and carotid atherosclerosis and stenosis. Elevated plasma total homocysteine (tHcy) levels have been indicated as a risk factor for coronary heart disease [8,9,10], ischemic stroke[11, 12], and peripheral artery disease [13, 14]. Also, studies have related tHcy levels to carotid atherosclerosis as a surrogate end point for cardiovascular diseases [15, 16]. However, most of these findings were derived from white populations, and whether such findings also apply for Asians remains to be determined. Current study was conducted to evaluate the association of serum Homocysteine with carotid stenosis in patients of ischemic stroke. In this study thirty six patients of ischemic stroke was enrolled as case and equal number of age-sex matched normal healthy adult were taken as controls. Mean age of the cases were 50.28 ± 14.29 years and controls were 51.08 ± 14.50 years, with no significant difference between two groups. Most of the subjects were from age group between above twenty to eighty years. In two previous same type of study was done to explore the association of homocysteine with carotid stenosis , the mean age of one study was 66 years[15],and in other study it was 66.2 ± 11.0 years[17].

Diabetes mellitus, hypertension and ischemic heart disease, family history of hypertension and diabetes mellitus, smoking are considered as significant risk factors of stroke and carotid atherosclerosis. In some of the studies that are limited in number, any association with known risk factors has not been determined [18]. In numerous studies, elevated homocysteine levels were found to be significantly correlated and associated with smoking, male gender, hyperlipidemia and hypertension [19.20].

In present study mean serum fasting sugar, serum fasting lipid profile (TC) and serum LDL was significantly higher among cases, but serum HDL and triglyceride (TG) had no such difference. In a series mean (± standard deviation) of total cholesterol, triglyceride, HDL-C, LDL-C and VLDL-C in patients and control group summarized had no statistical difference [21].

Hyperhomocystenaemia defined an elevated homocysteine concentration as one that exceeds 15.8 mmol per liter (95th percentile for healthy control subjects) [22]. Other defined an elevated homocysteine concentration as one that exceeded 13.9 mmol per liter (the mean value plus 2 SD among healthy young controls) [23]. In the Framingham Heart Study cohort had previously considered a homocysteine concentration of 14 mmol per liter to be elevated (90th percentile for persons with apparently adequate concentrations of folate, vitamin B12, and vitamin B6) [24]. In current study, serum fasting total plasma homocysteine level in case group was 21.89 ± 9.38 ìmol/l which was significantly higher than the controls (12.31 ± 3.27 ìmol/l), (p=0.001).

In a series the median concentration of total homocysteine was 16.4 mmol/L among cases versus 14.3 mmol/L among controls [25]. Concentrations of total homocysteine were higher in two thirds of the matched pairs in the case subjects [26].

In current study 25.0% of cases serum total homocysteine level was normal and in 75.0% of cases it was elevated. In control group in 83.33% respondents it was within normal level and 16.67% elevated. Homocysteine level was significantly higher among cases (p=0.001). In a recent study the homocysteine concentration was found within the normal levels in 35.4% of the patients, it was found to be lightly elevated in 56.3% of the patients and moderately elevated in 8.3%. The homocysteine level in the control group was found to be within normal levels for 90% of the control subjects; and only 10% of the control subjects displayed lightly elevated levels of homocysteine ($p<0.01$) [21]. In a study, total homocysteine level was normal in 71.5% of stroke cases and elevated in 28.5% [27]. Serum total cholesterol (TC), LDL had a positive correlation with serum homocysteine with a p value 0.001. Serum HDL had a negative correlation and TG had a positive with no statistical significance.

In present series we have determined 36.1% cases had small artery disease, 38.9% large artery disease, 8.3% cases cardioembolic and in 16.7 %

other causes. Fujishama reported that as a manifestation of cerebral small-artery diseases, lacunar infarction is the most prevalent type of ischemic stroke in Japanese people[28]. In the studies carried out in relation with etiological correlations, Eikelboom and colleagues have found in a case-control study that hyperhomocysteinemia is associated in particular with stroke due to large-vessel atherosclerosis. However, it was found to be less associated with small-artery disease and any correlation with CE or other etiologic subgroups has not been determined which was consistent with our current study[29].

To further examine the link between carotid atherosclerosis and tHcy levels, multiple regression analysis was performed. When traditional atherosclerotic risk factors were controlled for, tHcy was found to be significantly associated with plaque score, suggesting a potential effect of higher tHcy in the evolution of carotid atherosclerosis. This finding is consistent with a previous study showing associations between tHcy and carotid plaque area [17].

According to extracranial carotid duplex study current series shows that normal finding was found in seven cases(19.4%), Group 1 finding was found in seven cases(19.4%), group 2 findings in eight cases(22.2%), group 3 findings in thirteen cases(36.1%) and group 4 findings in one case(2.8%).In present study we have found five cases with normal level of homocysteine and two with elevated homocysteine had normal Doppler findings (p=0.056), one case with normohomocysteinemic cases and six of hyperhomocysteine cases had group 1 findings (0.001), one case with normo-homocysteinemic cases and seven with hyperhomocysteinemic cases had group 2 findings (p=0.001), two with normal homocysteine and eleven with higher homocysteine had group 3 findings (p=0.001) and one of hyper homocysteinemic patients had group 4 findings. All abnormal Doppler findings were significantly higher among cases with elevated level of homocysteine (p=0.001, 0.001, 0.001). Elevated total homocysteine concentrations were found to be associated with carotid artery wall thickening and stenosis; and hyperhomocysteinemia and the ischemic events with manifestations of significant carotid stenosis were considered as independent risk factors [15]. Malinow et al reported that fasting plasma levels of homocysteine were significantly higher in 287 subjects with thickened intimal-medial carotid walls than in control subjects[15,30] performed a cross-sectional study of 1041 elderly subjects (418 men and 623 women; age range, 67 to 96 years) from the Framingham Heart Study, found that plasma homocysteine concentrations are associated with extracranial carotid-artery stenosis in a population-based cohort of elderly people [15]. Another study demonstrated that persons with carotid-artery walls whose thickness exceeded the 90th percentile for the study cohort had significantly higher fasting plasma homocysteine concentrations than persons with carotid- artery walls whose thickness was below the 75th percentile[16].

Although Mousavi et al, failed to demonstrate any meaningful difference in carotid stenosis between patients with normal and elevated tHcy levels is probably due to the low frequency of extracranial disease in the Asian population and homocysteine related atherosclerosis [31].

The current study demonstrated that higher level of homocysteine is significantly associated with carotid stenosis in patients of stroke and hyperhomocysteinemia is an independent risk factor for carotid stenosis in patients of ischemic stroke.

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Efficacy of Local Corticosteroid in Idiopathic Carpal Tunnel Syndrome: A Randomized Controlled Trial

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Abstract

Background: *Carpal tunnel syndrome (CTS) is a common health problem in Bangladesh especially among women. It causes significant morbidity and reduces work output in affected patients. There are few treatment options available like oral steroid, steroid injection, UST, surgical treatment etc. Considering the cost, time and consequence of surgery, short term nonsurgical management is desirable e.g. local steroid injection in the affected limb. Therefore a comparative analysis is necessary to understand the efficacy of local steroid injection.* ***Objective:*** *To evaluate the efficacy of local corticosteroid injection in the treatment of idiopathic carpal tunnel syndrome.* ***Methods:*** *60 idiopathic CTS patients divided into two groups by randomization. One group received Inj. Triamcinolone 30 mg close to carpal tunnel and other group received oral steroids. Efficacies of treatmemt were compared in between groups. Result: The mean age of two groups were 37.5 ± 10.5 and 37.0 ± 10.24 years respectively (p = 0.272) and Majority of the patients in both treatment groups (76.7% in local steroid and 80% in oral steroid groups, p = 0.754) were female. Relief from tingling sensation and nocturnal awakening was higher in the steroid injection receivers (100% and 86.7% respectively) than that in the oral steroid receivers (6.9% and 3.4% respectively) during evaluation of outcome at the end of 3 month. End point treatment shows that none but SNAP at wrist in the local steroid group improved significantly better than that in the oral steroid group (16.2 ± 10.5 vs. 12.4 ± 6.3, p =0.039). No major side effects occurred in local steroid group except depigmentation in injected area 3 (10%) cases.* ***Conclusion:*** *It may be concluded that local steroid injection is an effective treatment of idiopathic carpal tunnel syndrome. But long-term efficacy of steroid injection remains uncertain.*

Keyword: *Carpal Tunnel Syndrome, Corticosteroid, Electrophysiology*

Introduction

Now-a-days Carpal tunnel syndrome (CTS) is an emerging health problem in Bangladesh especially among middle and old age female population. It is the compression of the median nerve at the wrist (carpal tunnel) in absence of an obvious injury, trauma or surgery which causes significant morbidity and reduces work output in affected patients. Many patients have to change jobs or modify activities to decrease their symptoms[1,2]. Women are three times more likely to develop CTS than men. The prevalence of CTS in general Western European population has been estimated to be at 3% to 5.8% for women and 0.6% to 2.1% for men[3,4]. There are many therapeutic approaches for CTS; among them some are conservative, including avoiding excess use of hand, use of splint, oral steroid, local steroid, diuretics, oral pyridoxine therapy UST etc. Regarding non-conservative measures, surgery is the approach of choice.

Patients with CTS should avoid repetitive wrist and hand motions and if possible, should not use

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vibratory tools[5]. Ergonomic measures to relieve symptoms depend on the motion that needs to be minimized. Patients, who work on computers, may benefit from improved wrist positioning or the use of wrist support. In addition to wrist splinting, conservative treatments includes oral corticosteroid therapy and local steroid injections. Surgical decompression of median nerve at carpal tunnel is costly and has limited access. Oral corticosteroid has no or minimum evidence of long term efficacy rather than high dose oral corticosteroid use for prolonged period has many adverse effects. Local corticosteroid injection at carpal tunnel in patients with CTS improve symptoms in more than 75% of cases and has been superior to oral corticosteroid in randomized clinical trials. Wong et al.[6] have reported that local triamcinolone 30mg not only give symptomatic relieve but also improve distal motor (DML) and sensory (DSL) latencies of the median nerve. Most of the respondents maintained their response twelve months without any additional therapy.

So, considering the cost, time and consequence of surgery, short term nonsurgical management is desirable e.g. local steroid injection in the affected limb. Therefore a comparative analysis is necessary in this arena. As far as my knowledge goes previous studies on CTS have not focused on this particular issue in Bangladesh. If it is proved that this type of maneuver is effective for the patient in relief of symptoms, then it will be really helpful for the clinicians, researchers as well as health planners to contribute towards better management of CTS.

Objectives

- To evaluate the efficacy of local corticosteroid injection in the treatment of idiopathic carpal tunnel syndrome.
- To determine the period of symptom relief following corticosteroid injection into the carpal tunnel.
- To determine the extent of relief of symptoms.
- To compare the efficacy of local corticosteroid with oral corticosteroid in reducing symptoms by symptoms severity score and functional status score.
- To find out electrophysiological changes before and after treatment in both groups by functional status score.
- To determine the side effects of both modalities of treatment.

Materials & Methods:

This was a randomized controlled clinical trial carried out in the Department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU) starting from July 2008 to June 2010. Patients attending the outpatient of Department of Neurology, BSMMU, designated as clinically suspected CTS and established by electrophysiological parameters and treated in two groups. One group received Injection Triamcinolone 30 mg close to carpal tunnel once in a month and other group received oral steroids for one month. Patients who are idiopathic and age in between 12 to 70 years were included in the study. Patients with symptoms less than 3 months and who has CTS-like condition such as cervical radioculopathy, proximal median neuropathy or significant polyneuropathy and with hypothyroidism, diabetes mellitus, pregnancy, cognitive impairment, vibrating tool users, muscle wasting and with recent peptic ulcer disease or history of steroid intolerance were excluded from the study. Selected subjects were randomly assigned to local steroid injection and oral steroid group. All relevant information from history, clinical examination and investigations were collected in a semi-structured data collection sheet. Collected data were processed and analyzed by using computer based software, statistical package for Social Science (SPSS).

Observation & Results

Among total 60 cases of carpal tunnel syndrome majority of the patients in both treatment groups (76.7% in local steroid and 80% in oral steroid groups) were female (p=0.754). Age distribution was almost similar in both the treatment groups and mean age of the local steroid and oral steroid groups were 37.5 ± 10.5 and 37.0 ± 10.24 years respectively (p = 0.272). Distribution of the patients by affected hands between groups is more or less similar (p = 0.575). Ninety percent of the patients of local steroid injection group had been suffering

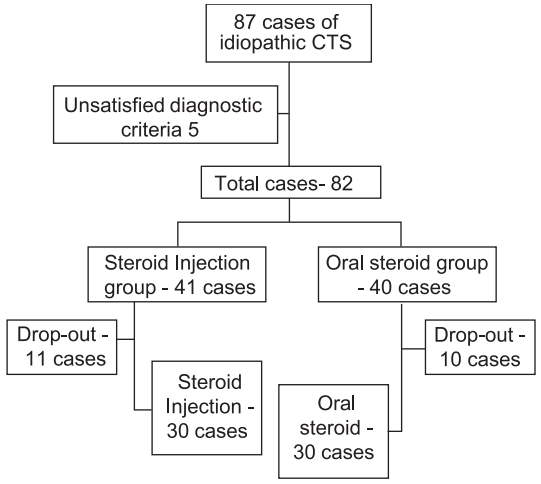

Fig.-1. *Flow diagram of the subject progress through the phases of the study. A total of 87 cases clinically diagnosed a idiopathic CTS were selected for the study. Among them 82 cases satisfied diagnostic criteria. Then 41 cases randomly selected for local steroid injection and 40 for oral steroid. During follow-up of three months 11 cases who took injection steroid and 10 cases who took oral steroid were dropped out. So, finally 30 cases of both groups were studied.*

from Carpal Tunnel Syndrome for > 6 months at entry compared to 66.7% of the oral steroid group (p = 0.002). Comparison of clinical characteristics of the patients between groups shows that tingling was invariably present in both the treatment groups (p = 0.029). Seventy percent of the local steroid injection receivers and 53.3% of the oral steroid receivers had persistent numbness (p = 0.31). No significant difference was observed between the groups in terms of nocturnal increase in symptoms with consequent awakening (p = 0.500), Phalen's maneuver (p = 0.063) and Tinel's sign (p = 0.500). Symptoms severity score and functional status score were also identically distributed between the groups (p = 0.066 and p = 0.110 respectively). All the measures of electrophysiological variables pertaining to median nerve before intervention are analyzed and none of the variables but distal motor latency was observed to be significantly higher in the local steroid injection group compared to oral steroid group.

Evaluation of outcome at month 3 revealed that symptoms severity score and functional status score reduced significantly in both the study groups from their baseline figures (p < 0.001) (Table I). Regarding electrophysiological parameters in local steroid group DML and DSL at wrist were reduced, while CMAP and SNAP were increased significantly at month 3 from their baseline figures (p <0.001, p < 0.001, p < 0.001 p = 0.009 respectively) (Table II). In oral steroid group no significant change was noted in terms of any of the 5 electrophysiological variables (p > 0.05 in each case) (Table II).

Evaluation of outcome 3 months after intervention demonstrates that 100% of local steroid injection receivers got relief from tingling sensation in the affected hand (p = 0.22) as opposed to only 6.9% of the oral steroid receivers (p < 0.001). Relief from nocturnal awakening was also appreciably higher in the steroid injection receivers (86.7%) than that in the oral steroid receivers (3.4%). Symptoms severity score and functional status score were also at much lower level in the former group than those in the latter group (p< 0.001 and p < 0.001 respectively). Relief of numbness was considerably higher in the former group than that in the latter group, though the difference was not statistically significant (p = 0.153) (Table III).

Table-I

Changes in clinical scores in both groups following intervention

Scores	Local Steroid Injection			Oral Steroid		
	Before intervention	After intervention	p-value[#]	Before intervention	After intervention	p-value[#]
	(n = 30)	(n = 30)		(n = 30)	(n = 30)	
Symptoms severity score[i]	26.8 ± 4.5	17.5 ± 5.2	< 0.001	31.4 ± 3.9	28.7 ± 3.8	< 0.001
Functional status score[i]	19.8 ± 3.1	12.5 ± 3.6	< 0.001	22.8 ± 3.9	19.6 ± 3.8	< 0.001

[i] Data was analyzed using Paired t-Test and were presented as Mean ±SD.

Table-II

Changes in electrophysiological parameters in both groups following intervention

Electrophysiological variables	Local Steroid Injection			Oral steroid		
	Before intervention (n = 30)	After intervention (n = 30)	P-value#	Before intervention (n = 30)	After intervention (n = 30)	P-value#
DML (ms)	6.7 ± 2.09	5.9 ± 1.53	< 0.001	5.75 ± 0.98	5.64 ± 1.0	0.091
CMAP (mV)	7.5 ± 2.4	8.5 ± 2.17	< 0.001	8.10 ± 3.04	7.9 ± 3.0	0.122
MNCV (m/s)	50.5 ± 3.7	50.6 ± 3.6	0.69	50.78 ± 3.97	50.64 ± 3.7	0.273
DSL at wrist (ms)	3.20 ± 1.3	2.7 ± 1.1	< 0.001	2.91 ± 1.21	2.9 ± 1.2	0.407
SNAP at wrist (μV)	14.2 ± 10.2	16.2 ± 10.5	0.009	12.7 ± 6.5	12.3 ± 6.3	0.066

Data were analyzed using Paired t-Test and were presented as Mean ± SD.

Table-III

Clinical outcome 3 months after intervention between groups

Outcome variables	Group		p-value#
	Local steroid injection (n = 30)	Oral steroid (n = 30)	
Relief of tingling†	30 (100.0)	2 (6.9)	< 0.001
Relief of numbness#	12 (40.0)	7 (24.1)	0.153
Relief from nocturnal awakening#	26 (86.7)	1 (3.4)	< 0.001
Symptom severity score¶	17.5 ± 5.26	28.7 ± 3.85	< 0.001
Functional status score¶	12.5 ± 3.6	19.6 ± 3.84	< 0.001

Data was analyzed using Ç2 Test; †Data was analyzed using Fisher's Exact Test;

¶ Data was analyzed using Student's t-Test and was presented as Mean ± SD.

No major side effects occurred in local steroid group except 3(10%) depigmentation in injected area. In oral steroid group 6 (20%) nausea, 3 (10%) epigastric pain, 1 (3.33%) leg oedema, and 1(3.33%) raised blood pressure occurred.

Discussion:

Carpal Tunnel syndrome is a very common problem encountered in Bangladesh. This hospital based study and was carried out to see the efficacy of local steroid over systemic steroid. Age distribution was almost similar in both the treatment groups with peak age incidence being observed in between 3rd and 4th decades of life (43%). Agarwal et al.[7] observed the highest percentage (51%) of both groups were 4th decade of life. Majorities of the patients in both treatment groups (76.7% in local steroid and 80% in oral steroid groups) were female. Padua et al.[8] observed same in both groups (71% in local steroid and 73% in oral steroid groups). It revealed that two-third cases of both groups had right hand affected and very few patients had both hands affected. Most of the studies including Shekhar et al.[9] also found the same. Most of the patients had been suffering from Carpal Tunnel Syndrome for > 6 months at entry which is also supported by other studies.

Comparison of clinical characteristics of the patients between groups shows that tingling was invariably present in both the treatment groups (p=0.029). Seventy present of the local receivers and 53.3% of the oral steroid receivers had persistent numbness (p=0.31). But evaluation of outcome 3 months after intervention demonstrates that 100% of local steroid injection receivers got relief from tingling sensation in the affected hand (p = 0.22) as opposed to only 6.9% of the oral steroid receivers (p < 0.001). This result is quite consistent with that of the study done by Agarwal et al[7]. Relief of numbness was also better for local steroid group as 40% compared to oral steroid group 24.1%. But there was no significant difference in between groups regarding relieve of numbness. But Goyal et al.[10] found significant difference regarding relief of numbness between local steroid group and oral steroid group. Relief from nocturnal awakening was appreciably higher in the steroid injection receivers (86.7%) then that in the oral steroid receivers (3.4%). There was significant difference between the groups. Singh

et al.[11] also found the significant difference between groups regarding Relief from nocturnal awakening. In this study it was revealed that symptom severity scale and functional status scale was significantly reduced after three months following intervention (In all cases p<0.001) in both groups. Shekhar et al.[9] also found significant difference in both groups. From local steroid group DML (ms) and DSL W (ms), was reduced significantly after 3 months following intervention than before intervention. But in oral steroid group there is no significant difference between before and after intervention. Padua et al.[8] also observed significant difference in local steroid group and no significant difference in oral steroid group regarding DML (ms) and DSL W (ms) in between before intervention and 3 months following intervention. On the other hand CMAP (mv) and SNAP W (¼v) was increased significantly from before intervention to three months following intervention in local steroid group. In oral steroid group those were not significantly increased before and after intervention. Padua et al.[8] also observed significant difference in local steroid group and no significant difference in oral steroid group regarding CMAP (mv) and SNAP W (¼v). The study revealed that no major side effects occurred in local steroid group except depigmentation in injected area in 10% cases. But in oral steroid group nausea, epigastric pain, leg oedema, and raised blood pressure occurred. Agarwal et al.[7] also found depigmentation in injected area in some patients in local steroid group and various types of side effects such as nausea, epigastric pain, leg oedema and hirsutism in oral steroid group.

Some wide variability in response to local steroid injection probably is due to the heterogeneity of the patients in terms of their symptoms, severity, functional impairment and natural history and outcome assessments. From all these discussion it appeared from our data, that relief of symptoms, will support the case for a policy of treating CTS patients with local corticosteroid injections rather than oral corticosteroid. This study showed a clear benefit from steroid injection versus oral steroid in the treatment of CTS. Steroid injection is a safe, easy to perform and effective short-term treatment in CTS.

In this study sample size was small due to time and resource constraint. Random sampling technique was also not followed. Single follow-up is another limitation of this study. It would have been better if multiple follow-up could have been done.

Conclusion:

It may be concluded that local steroid injection is an effective treatment of idiopathic carpal tunnel syndrome. But these studies have some limitations, i.e regarding long-term efficacy of steroid injection remains uncertain. In case of mild to moderate idiopathic carpal tunnel syndrome, every patient should be treated with local steroid injection and should be considered before surgical decompression. This study would stimulate the necessity of further study in a large scale in future; which may be helpful for clinicians, researchers, as well as health planners to contribute towards better management of CTS.

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Genetic testing for Spinocerebellar Ataxias (SCA) in Parkinsonism

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Abstract:

Objective: *The study was conducted to find out Spinocerebellar Ataxias (SCA) by genetic analysis from those presenting with parkinsonism in the Neurology department of Mymensingh Medical College.* ***Materials and methods:*** *A sample of about 5ml blood was collected by venipuncture in EDTA tube with informed consent from the patients following institutional ethics committee approval by genetic study from 7 healthy people and 9 patients. The neurological disorder along with a complete physical and/or psychological, as well as family history and demographic data was recorded with a prescribed questionnaire by the neurologists of Mymensingh Medical College. Extraction of genomic DNA from the venous blood using FlexiGene DNA kit (Qiagen, Japan) was performed in Department of Medicine, Bangladesh Agricultural University, Mymensingh 2202, Bangladesh. The extracted DNA was stored and accumulated and then these DNA were sent to Division of Clinical Genetics, Department of Medical Genetics, Osaka University Medical School, Suita, Osaka 565 0871, Japan for PCR and further analysis. PCR amplification of the CAG repeat was performed for the SCA1, SCA2, SCA3, SCA6 loci using primers SCA1N-F1 and SCA1N-R1, SCA2-F1 and SCA2-R1, MJDF1 and MJDR1, SCA6-F1 and SCA6-R1, respectively.* ***Results:*** *SCA1 PCR of both healthy individual and suspected PD patients DNA is about 250 bp (no. of CAG repeats=36). SCA2 PCR products reveal the DNA products of about 150 bp (no. of CAG repeats=23) except one patient that we suspected and it was sequenced and revealed 175bp (no. of CAG repeats=30). SCA3 PCR product size of both healthy individual and patient DNA is within about 250 (no. of CAG=11) to 300 bp (no. of CAG repeats=28) except one patient which is about 320bp and its CAG repeats is about 34. SCA6 PCR product size of both healthy individual and patient DNA is about 150bp (no. of CAG=16).* ***Conclusion:*** *This is the first time from Bangladesh regarding the range of CAG repeats in patients as well as healthy individual.*

Key words: *Spinocerebellar ataxias (SCA), parkinsonism, genetic testing*

Introduction:

The autosomal dominant spinocerebellar ataxias (SCAs) are a complex group of neurodegenerative disorders characterized by progressive cerebellar ataxia of gait and limbs variably associated with ophthalmoplegia, pyramidal and extrapyramidal signs, dementia, pigmentary retinopathy and peripheral neuropathy[1]. There are several subtypes of SCAs: SCA1, SCA2, Machado-Joseph disease (MJD)/SCA3, SCA6, SCA7, SCA17 (Table 2). In all cases, expansion of CAG/ repeats in the respective genes have been implicated in the pathogenesis of the disease[2-10]. For example, the number of CAG repeats at the SCA1 locus varies

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from 25 to 36 in normal individuals, while among affected individuals the range is 40 to 81[5]. Similarly, polymorphic CAG repeats in the ataxin2 gene (SCA2 locus) varies from 15 to 29 repeats among normal individuals and from 35 to 59 among affected individuals[3,9].

Wide global variation in relative prevalence of SCA subtypes among autosomal dominant cerebellar ataxia (ADCA) patients has been observed. SCA1 has been reported to be far more common in Russia[11] than any other SCA subtypes. Recently Takano et al[12] have reported that the general prevalence of SCA1 and SCA2 is significantly higher among white SCA pedigrees (15% and 14%, respectively) than in the Japanese (3% and 5% respectively), whereas relative prevalence of SCA3 is higher in the Japanese pedigrees (43%) than in whites (30%). Also, SCA6 appear to be less frequent in white populations (5%) than in Japanese populations (11%) respectively[12] It has been reported that SCA2 is exclusively responsible for all ataxia cases in the Indian population[13]. In a study of six Indian SCA2 pedigrees, Wadia et al[13] observed CAG repeat expansion in 14 affected family members at the SCA2 locus. All of these patients showed slow saccades and peripheral neuropathy. An inverse correlation between repeat size and age at onset was observed with repeat numbers varying from 36 to 45 repeats[13]. Similar observation has been reported by Saleem et al[14] in an independent set of 39 SCA pedigrees principally from northern India. SCA2 is also the most common form of hereditary ataxias among Korean patients[15], constituting 12.6% of all SCA patients, followed by SCA6 (6.9%) and SCA3 (4.6%).

SCA3 is more common in Germany[16], Brazil[17] United States[18,19], Portugal[20] and Japan[21]. In Portugal, expansion at SCA3/MJD locus was observed in 74% of ADCA patients, followed by expansion at SCA2 locus in 4% of patients. The investigators did not find any SCA1, SCA6 mutation[20]. Similarly, in the Japanese population, Sasaki and Tashiro[21] have observed that 24.6% of patients possessed CAG expansion at the SCA3 locus, followed by expansions at SCA6 (11.8%), SCA1 (10.5%) and SCA2 (4.4%) loci. SCA6 is the most common (5%) expansion mutation in SCA patients in the United Kingdom, followed by SCA2[22]. Expansion at the SCA6 locus is also very frequent (13%) in ADCA families of Germany[23]. Spinocerebellar ataxia type 3 (SCA3), can present with parkinsonism. However, classically, atypical features, including pyramidal and cerebellar signs, peripheral neuropathy, and/or anterior horn cell dysfunction, are also seen[24]. To our knowledge, there are no previous reports of regarding the CAG repeat in patients as well as healthy individuals in Bangladesh. In this study we present the results of DNA analysis of CAG repeats in the healthy individual and as well as patients provisionally diagnosed as Parkinson Disease (PD) in Department of Neurology, Mymensingh Medical College, Mymensingh-2200, Bangladesh.

Materials and Methods:

A sample of about 5ml blood was collected by venipuncture in EDTA tube with informed consent from the patients following approval by institutional ethics committee for genetic study from 7 healthy people and 9 patients who came to Department of Neurology, Mymensingh Medical College, Mymensingh 2200, Bangladesh. The neurological disorder along with a complete physical and/or psychological, as well as family history and demographic data (sex, age at onset, age at referral, residence) was recorded with a prescribed questionnaire by the neurologists of Mymensingh Medical College. Extraction of genomic DNA from the venous blood using FlexiGene DNA kit (Qiagen, Japan) was performed in Department of Medicine, Bangladesh Agricultural University, Mymensingh 2202, Bangladesh. Briefly, pipetting of 7.5 ml Buffer FG1 into a 15 ml centrifuge tube and then adding of 3 ml whole blood and mixing by inverting the tube 5 times. Centrifuging for 5 min at 2000 x g in a swing-out rotor and discarding the supernatant and leaving the tube inverted on a clean piece of absorbent paper for 2 min, taking care that the pellet remains in the tube. Adding of 1.5 ml Buffer FG2, closing the tube, and vortexing immediately until the pellet is completely homogenized. Inverting the tube 3 times, placing it in a heating block or water bath, and incubate at 65 degree C for 10 min. Adding of 1.5 ml isopropanol (100%) and

mixing thoroughly by inversion until the DNA precipitate becomes visible as thread or a clump and centrifuging for 3 min at 2000 x g. Discarding the supernatant and briefly invert the tube onto a clean piece of absorbent paper, taking care that the pellet remains in the tube. Adding of 1.5 ml 70% ethanol and vortex for 5 second and centrifuging for 3 min at 2000 x g. Discarding of the supernatant and leaving the tube inverted on a clean piece of absorbent paper for at least 5 min, taking care that the pellet remains in the tube. Air-drying the DNA pellet until all the liquid has evaporated and adding 300 microliter FG3, vortexing for 5 second at low speed, and dissolve the DNA by incubating for 1 hour at 65 degree C in a heating block or water bath and stored at -70 degree C until used.

The extracted DNA was stored and accumulated and then these DNA were sent to Division of Clinical Genetics, Department of Medical Genetics, Osaka University Medical School, Suita, Osaka 565 0871, Japan for PCR and further analysis. PCR amplification of the CAG repeat was performed for the SCA1, SCA2, SCA3, SCA6 loci using primers SCA1N-F1 and SCA1N-R1, SCA2-F1 and SCA2-R1, MJDF1 and MJDR1, SCA6-F1 and SCA6-R1, respectively (Table 1) and the condition for amplification were essentially same as described earlier[4,6,9,10,25]. PCR products were checked in 3% agarose gel and the sequencing of the suspected PCR products were performed using Genescan system (version 2.02) in an ABI-377 automated DNA sequencer.

Table-I

PCR Primer Sequences used in this study for detection of SCA1, SCA2, SCA3, SCA6 loci.

Primer	Sequences
SCA1N-F1	CTG GCC AAC ATG GGC AGT CTG AG
SCA1N-R1	GGA GAA CTG GAA ATG TGG ACG TA
SCA2-F1	CCC TCA CCA TGT CGC TGA AGC
SCA2-R1	CGA CGC TAG AAG GCC GCT G
MJD-F1	CCA GTG ACT ACT TTG ATT CG
MJD-R1	CTT ACC TAG ATC ACT CCC AA
SCA6-F1	CAC GTG TCC TAT TCC CCT GTG ATC C
SCA6-R1	TGG GTA CCT CCG AGG GCC GCT GGT G

Table-II

Different types of SCA with its gene range of CAG repeat and affected regions.

Diseases	Gene	CAG repeat		Affected regions
		Normal	Disease	
spinocerebellar ataxia type 1 (SCA1)	ataxin-1	6-44	39-83	Cerebellar Purkinje cells, dentate nucleus, brainstem
spinocerebellar ataxia type 2 (SCA2)	ataxin-2	15-31	36-63	Cerebellar Purkinje cells, brainstem
spinocerebellar ataxia type 3 (SCA3) /Machado-Joseph disease	ataxin-3	12-41	55-84	Dentate nucleus, basal ganglia, brainstem, spinal cord
spinocerebellar ataxia type 6 (SCA6)	? 1A calcium channel	4-18	21-33	Cerebellar Purkinje cells
spinocerebellar ataxia type 7 (SCA7)	ataxin-7	4-35	37-306	Cerebellar, brainstem, retina
spinocerebellar ataxia type 17 (SCA17)	TATA-binding protein	25-44	46-63	Cerebellar, cerebral cortex, basal ganglia

Results and Discussion:

SCA1 PCR of both healthy individual and suspected PD patients DNA is about 250 bp (no. of CAG repeats=36) (Figure 1). SCA2 PCR products reveal the DNA products of about 150 bp (no. of CAG repeats=23) (Figure 2) except one patient that we suspected and it was sequenced and revealed 175bp (no. of CAG repeats=30) (Figure 3). SCA3 PCR product size of both healthy individual and patient DNA is within about 250 (no. of CAG=11) to 300 bp (no. of CAG repeats=28) except one patient which is about 320bp and its CAG repeats is about 34 (Figure 4). SCA6 PCR product size of both healthy individual and patient DNA is about 150bp (no. of CAG=16) (Figure 5).

The polyglutamine diseases are a group of inherited neurodegenerative diseases caused by the expansion of a CAG repeat coding for glutamine in each disease-causing gene. Currently there is no effective treatment against the polyQ diseases. In

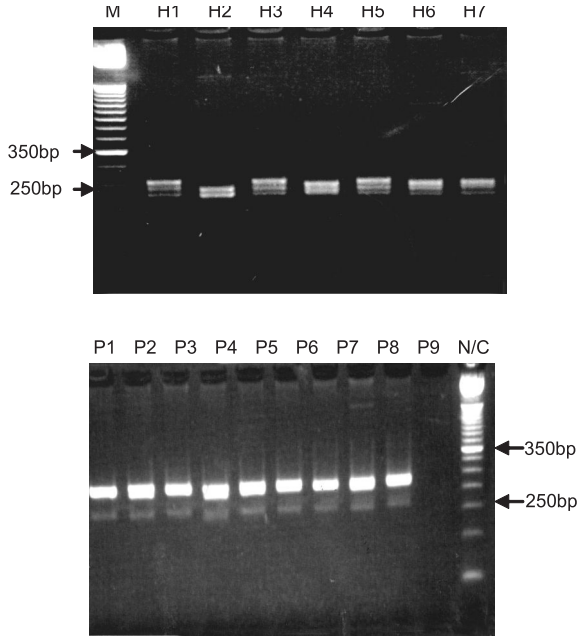

Fig.-1: *SCA1 PCR of 7 healthy individuals DNA (above) and 9 patients DNA (below): the PCR product size of both healthy (H1-H7) and patient DNA (P1-P9) is about 250bp (no. of CAG repeats=36) and therefore revealed no difference between the healthy individual and patient DNA, N/C= negative control, M= molecular marker.*

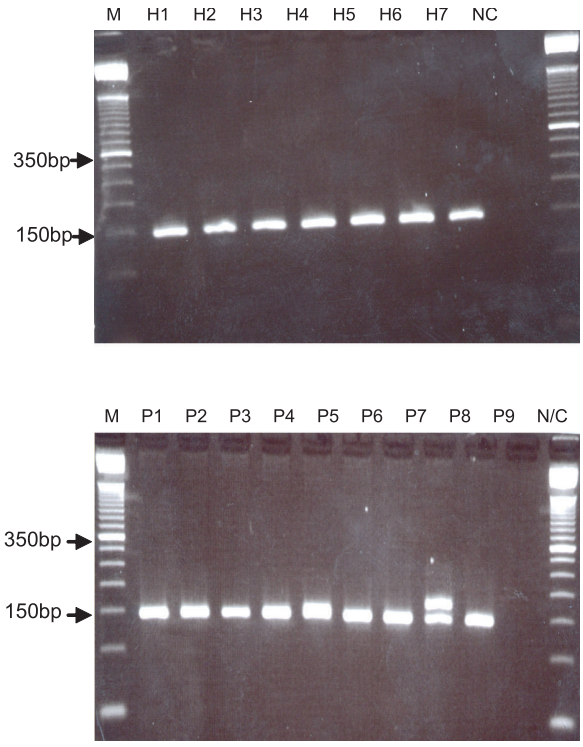

Fig.-2: *SCA2 PCR of 7 healthy individuals DNA (above) and 9 patients DNA (below): the PCR product size of both healthy (H1-H7) and patient (P1-P9) DNA is about 150bp (no. of CAG repeats=23) except no. 8 of patient sample which is about 175bp and this product was sequenced and it revealed 30 CAG repeats that is within the normal range, N/C= negative control, M= molecular marker.*

the pathogenesis of the polyQ diseases, expansion of the polyQ stretch is thought to cause misfolding of the protein, resulting in pathogenic protein-protein interactions including aggregate formation, leading to neuronal dysfunction and eventual neuronal death. Although extensive research has been performed regarding polyQ-mediated neuronal cell death, recent detailed analyses of brains of polyQ disease patients as well as mouse models have revealed that neuronal phenotypes develop before marked cell death is observed[26]. SCA is one of several polyglutamine diseases.

The first genetically documented family with MJD (SCA3) in India was reported by Chakravarty et al[27]

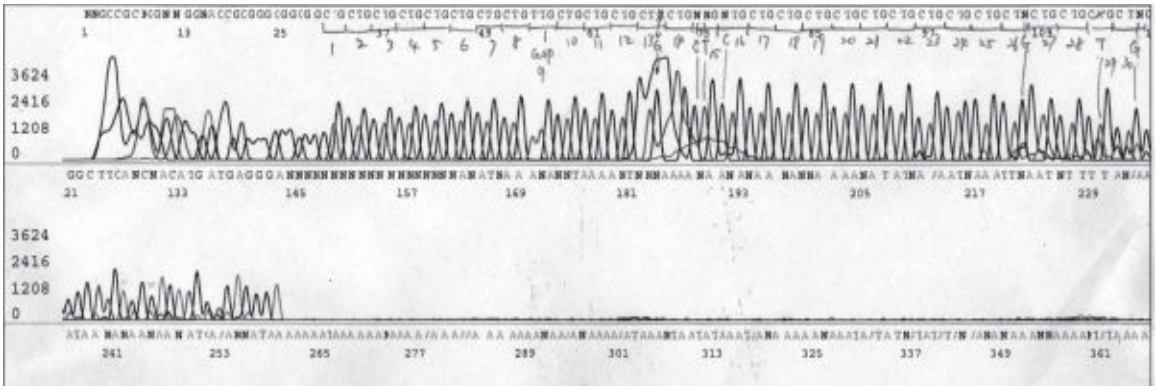

Fig.-3: *Sequenced data SCA2 PCR products from one patient (patient no. 8 that was suspected of SCA2 and it revealed 175bp (no. of CAG repeats=30).*

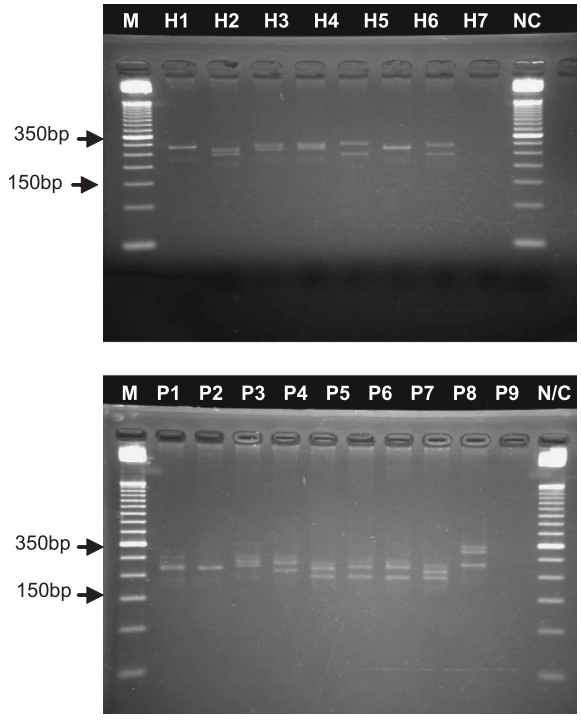

Figure 4: SCA3 PCR of 7 healthy individuals DNA (above) and 9 patients DNA (below): the PCR product size of both healthy (H1-7) and patient (P1-P9) DNA is within about 250 (no. of CAG repeats=11) to 300bp (no. of CAG repeats=28) except no. 9 of patient which is about 320bp and its CAG repeats no. is about 34 that not pathogenic (pathogenic range is 62-79 in India), N/C= negative control, M= molecular marker.

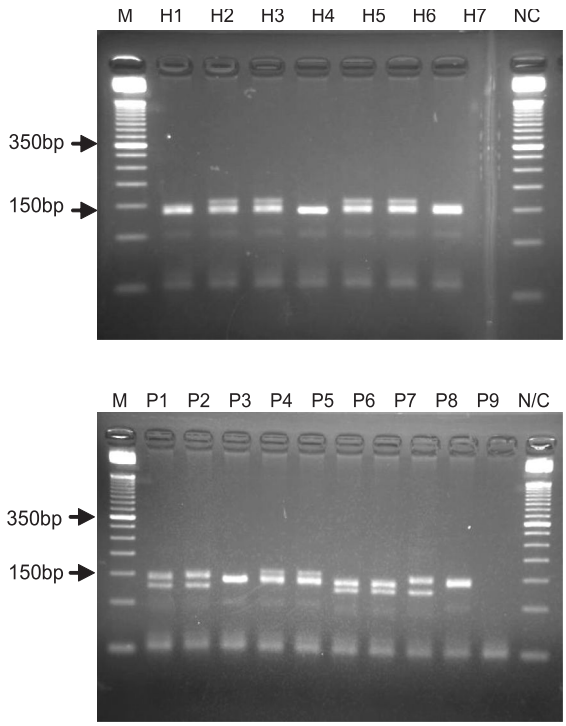

Fig.-5: *SCA 6 PCR of 7 healthy individuals DNA (above) and 9 patients DNA (below): the PCR product size of both health (H1-H7) and patient DNA (P1-P9) is about 150bp (no. of CAG repeats=16) and therefore revealed no difference between the control and patient DNA, N/C= negative control, M= molecular marker.*

in 1996 among Bengali family. Subsequently, genetic studies in families with cerebellar ataxias have been made by Wadia et al[13,28] in Mumbai and Sinha at Ranchi[29] and updated reviews on the subject have been written by Sinha[30], Banerjee and Chakravarty[31] and Wadia[32]. More recently two multiauthored communications highlighted on the molecular genetic aspects of autosomal dominant herediatary ataxias in India including Bengali family[14,33]. Basu et al[33] detected CAG repeat expansion in 6 patients (10.5%) at the SCA1 locus (range of expanded CAG repeat no. 44-52), ten of the 57 patients (17.5%) had CAG repeat expansion at the SCA2 locus (range of expanded CAG repeat no. 39-45), while four (7%) had CAG expansion at the SCA3/MJD locus (range of expanded CAG repeat no. 62-79) and at the SCA6 locus there was a single patient (1.8%) with 21 CAG repeats. Ghosh et al[34] reported five ethnic Bengali subjects with positive family history and found 3 cases of SCA1, 2 with SCA3 mutation and none with SCA2. Chakravarty and Mukherjee[35] also reported SCA in Ethnic Bengali; 2 families with SCA1, 4 families with SCA2, 5 families with SCA3 but there are no reports yet from Bengali population in Bangladesh (peoples in Bangladesh & West Bengal, a State of India are known as Bengali).

Bangladesh and India are in the same geographical region and it was the same country until the year 1947 but the people are not necessarily genetically akin. In this study we had examined 7 healthy individual in Mymensingh and 9 patients who came to the neurologists of Mymensingh Medical College and were diagnosed as Parkinson Disease. The age group of all the patients were 57-80 and all the patients has the tremor and most of patients has the tendency to fall down and memory impairment. Spinocerebellar ataxia type 3 (SCA3), can present with parkinsonism. However, classically, atypical features, including pyramidal and cerebellar signs, peripheral neuropathy, and/or anterior horn cell dysfunction, are also seen[24]. The patients diagnosed as PD were both male and female and they have other complaints but all are diagnosed as PD by the neurologists in Mymensingh Medical College.

The SCA1 PCR product size of both healthy individual and patient DNA is about 250bp (no. of CAG repeats=29) and therefore revealed no difference between the healthy individual and patient DNA. The SCA2 PCR product size of both healthy individual and patient DNA is about 150bp (no. of CAG repeats=23) except no. 8 of patient sample which is about 175bp and this product was sequenced and it revealed 30 CAG repeats that is within the normal range. The SCA3 PCR product size of both healthy individual and patient DNA is within about 250 (no. of CAG repeats=11) to 300bp (no. of CAG repeats=28) except no. 9 of patient which is about 320bp and its CAG repeats no. is about 34 but not pathogenic (pathogenic range is 62-79 in India). The SCA6 PCR product size of both healthy individual and patient DNA is about 150bp (no. of CAG repeats=16) and therefore revealed no difference between the healthy individual and patient DNA.

Spinocerebellar ataxia type 3 (SCA3), can present with parkinsonism but has not been previously reported, to our knowledge from Bangladesh. However, atypical, though also levodopa-responsive, parkinsonism has been previously reported to occur in African American families, suggesting that that this phenotype is associated with African ancestry. In this regard, it is perhaps significant that all the individuals with parkinsonism have relatively low numbers of repeats (normal, 16-34; pathologic, 60-84). In families in which linkage analysis is being performed to determine a locus for autosomal dominant parkinsonism suggestive of PD, evaluation for the *MJD/SCA3* mutation is indicated. In our study in Bangladesh we never recorded any CAG repeat within the pathological ranges. This is the first time from Bangladesh regarding the range of CAG repeats in patients as well as healthy individual.

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Anterolateral Retroperitoneal Approach of Thoraco-lumbar Spine; A Study of 20 Cases

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Abstract:

This cross sectional study was done from April 2005 to November 2009 in the department of Neurosurgery of Chittagong Medical College Hospital. We have studied 20 patients of D_{12}, L_1, L_2 & L_3 fracture with lower limb weakness. Data were collected by a brief history, clinical examination, surgery & postoperative follow up. Most of the sufferers were male (90.00%). The age groups were 21-40 years gripped the major proportion (50.00%) of the patients. The commonest causes of injury were fall from height (60.00%). The majority of patients had been suffering from L_1 fracture (45.00%). The most (90.00%) of the sufferers had parapareses. The highest groups of patients (90.00%) improved after surgery. So, the study concludes that the anterolateral decompression, fusion & fixation is one of the best options of treatment of throracolumbar spine fracture.

Key words: *Anterolateral retroperitoneal, thoracolumber spine.*

Introduction:

Anterolateral retroperitoneal approach is a easy approach specially for the surgeons those who are oriented with abdominal surgery. In this procedure anterior decompression can done by direct vision to the thecal sac. In case of lumbar or thoracic spine injury where posterior column of spine remains intact, no need to destroy posterior column. For this advantage we inspired to do the study to see the outcome after surgery.

The introduction of the anterior approach to the lumbar spine was initially designed for treatment of tuberculosis. In 1934, Ito and associates[1] reported on the replacement of a diseased vertebral body by using either tibial or rib autograft. Hodgson and colleagues[2-4] obtained international recognition when they described the anterior surgical approaches to the spine and reported on Pott's disease using anterior spinal fusion surgery. Subsequently Kelly and Whitesides[5], Fountain[6], and HohIman and Eismont[7] have applied the surgical principles to the management of trauma to the spine. Other authors have described anterior spinal surgery for various other conditions[8-10].

The retroperitoneal approach was developed from the standard flank incision that had been used for lumbar sympathectomies. In the 1950s, Harmon popularized its application to spinal surgery, using this exposure to fuse the lumbar spine in the treatment of degenerative disk disease[11]. Compared with the transpertioneal route, the retroperitoneal approach provides the necessary exposure of the vertebral bodies and decreased risk of visceral and vascular injury. Unlike the lateral extracavitary approach, this exposure requires no manipulation of nerve roots and avoids the destabilizing effects of dissecting the posterior musculature. Its disadvantages include unilateral

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exposure and the anatomic obstacles encountered if a right-sided approach is required. Despite these limitations, the retroperitoneal approach provides excellent visualization, allowing surgeons to identify the neural elements and thecal sac to gain access from L_2 through L_5. Either a midline or a lateral exposure can be used to enter the retroperitoneal space; the primary distinction is the position of the skin incision and the degree of muscle transaction.

Anterolateral Retroperitoneal Approach:

A flank incision is used to start the ventrolateral retroperitoneal approach. The patient is placed in a lateral decubitus position with appropriate padding to avoid pressure ulcerations and neuropathies. The patient is positioned so that flexion of the operating table opens the space between the iliac crest and costal margin. The incision begins in the postaxillary line between the ribs and iliac crest and follows an inferior oblique course to the lateral edge of the rectus sheath. The level of the incision depends on the desired level of exposure. For lesions of the upper lumbar spine, the incision should be made above the umbilicus along the 11^{th} or 12^{th} rib. The rib can be resected to improve exposure and to provide a substrate for a fusion. For lesions in the midlumbar spine, the incision starts at the level of the umbilicus. The lower lumbar spine is accessed through an incision superior to the midpoint, between the umbilicus and sysmphysis pubis. Exposure of the lumbosacral junction is obtained through an incision inferior to this point.

In reality it is an anterolateral view of the vertebrae that allows access to the segmental vessels, vertebral body, pedicle, and transverse process, as well as the spinal canal and its contents. Clinically, this approach is most commonly used in the treatment of fractures, infection, or tumours to anteriorly decompress the neural elements. It is also frequently used in scoliosis procedures in which anterior release with or without anterior interbody fusion is performed over several levels of the lumbar spine.

The retroperitoneal approach provides an anterolateral view of the spine and at L_4 and above the great vessels are not in the way. The iliac vessels do cross over the body of L_5 laterally in many patients, and access to the L_5 body and L_5-S_1 disk space can be limited with a retroperitoneal approach.

The skin incision is an oblique one that can be made over the 12^{th} rib or a few centimeters inferior to the 12^{th} rib. If access to T_{12} or L_1 is needed. Making the incision over the 12^{th} rib and removing it provides the best exposure in the upper lumbar area. For L_2 and lower, one can either remove the 12^{th} rib or make the incision halfway between the rib cage and the iliac crest. If one prefers the slightly higher incision, the 12^{th} rib is simply dissected out and removed; the remaining transversalis fascia is incised and this exposes the retroperitoneal space[12].

Materials & Methods:

The study was carried out in the department of Neurosurgery, Chittagong Medical College Hospital, Chittagong. The study was undertaken during April 2006 to November 2009.

Cases were selected following the inclusion & exclusion criteria

1. Inclusion Criteria:
   - Patients of either sex admitted with incomplete lumbar spine injury.
2. Exclusion criteria:
   - Those patients who were operated second time due to complication excluded in this study.
   - Complete injury.

Data was collected in a form regarding clinical presentation. Clinical examination, investigating procedure, postoperative evaluation & only those patients who gave consent were in concluded in the study.

Results:

Table-I

Distribution of patients by age (n=20)

Age in years	Number	Percentage
1-20	06	30.00
21-40	10	50.00
41-60	03	15.00
>61	01	5.00
Total	20	100.00

A total of 20 patients of different age group was selected.

It was revealed that the highest age groups were 21-40 years (50.00%). Only 5.00% were above 61 years age (Table I).

Table-II

Distribution of patients by causes of compressive fracture (n=20)

Causes	Number	Percentage
Fall from height	12	60.00
Road traffic accident	04	20.00
Fall of heavy object on back	02	10.00
Fall by Slepage of foot	01	05.00
Pathological fracture	01	05.00
Total	20	100.00

The table II showed that the causes of occurrence were fall from height (60.00%), road traffic accident (207), fall of heavy object on back (10%), fall by sleeping of foot (05%), pathological fractures (05%).

Table-III

Distribution of patients by site of compression (n=20)

Site	Number	Percentage
L_1	09	45.00
D_{12}	05	25.00
L_2	04	20.00
L_3	02	10.00
Total	20	100.00

From table III it was evident that the commonest site of compression was at L_1 vertebrae (45.00%), followed by D_{12} fracture (25.00%).

Table-IV

Distribution of patients by type of weakness (n=20)

Clinical features	Number	Percentage
Paraparesis	18	90.00
Monoparesis	02	10.00
Bladder dysfunction	10	50.00
Bladder & Bowel dysfunction	03	15.00
Sexual dysfunction	02	10.00
Bowel dysfunction	02	10.00
Bladder, Bowel & Sexual dysfunction	02	10.00
Intact autonomic function intact	01	05.00
Sensory function impaired	18	90.00

Table IV showed that the most of the sufferers had paraparesis (90.00%), the remaining 10.00% had monoparesis. The result revealed that the most of the patient (40.00%) had suffered from bladder dysfunction. In was documented that (90.00%) of the patients improved after surgery.

Table-V

Distribution of patients by type of modified MacNab's outcome score, autonomic function and sensory function outcome

MacNab's outcome score	Number	Percentage
Excellent (No pain)	08	40.00
Good (Occasional radicular pain)	09	45.00
Fair (Some improvement of functional capacity, still handicapped)	01	5.00
Poor (Continuous symptoms of root involvement)	02	10.00
Autonomic function		
Improvement of bladder function (n=10)	06	60.00
Improvement of bladder & bowel dysfunction (n=3)	01	33.33
Improvement of sex dysfunction (n=2)	01	50.00
Improvement of bowel dysfunction (n=2)	01	50.00
Improvement of bladder, bowel & sexual dysfunction (n=2)	01	50.00
Sensory function		
Improvement of sensory dysfunction (n=18)	16	88.89

The above table V showed the number of patients and the percentage according to MacNab's outcome score, autonomic function and sensory functions.

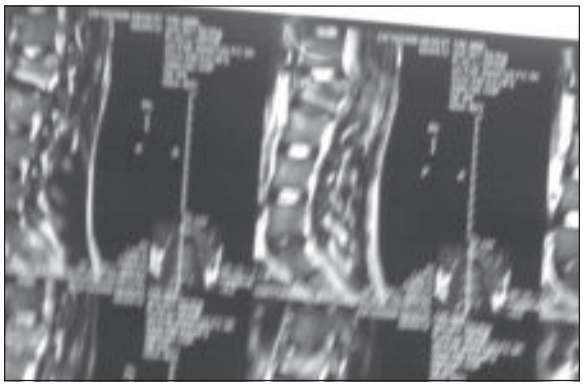

Fig.-1: *MRI of L/S Spine Shows Compressive fracture at L_2*

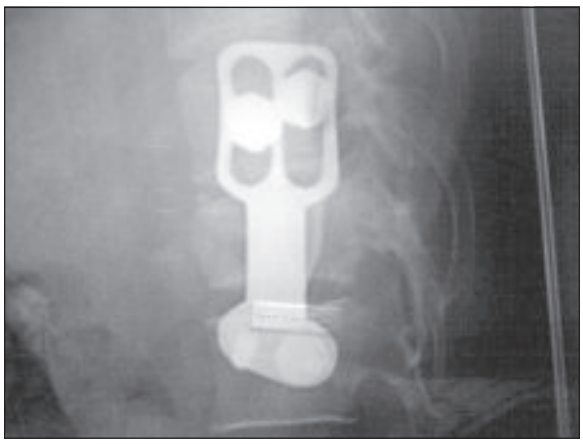

Fig.-2: *Another figure of Z plate fixation*

Discussion:

This is a cross sectional study. In this study the most of (90.00%) the sufferer were male. This study showed commonest age groups were 21-40 years (50.00%). In previous study commonest age groups were 21-40 years (75.00%)[13].

It was documented that male were affected more than female (90.00%). In previous study males (84.00%) were affected predominantly. Previous Authors mentioned that the commonest causes of injury were road traffic (60.00%)[13] accidents. In this study commonest causes of injury were fall from height (60.00%).

In previous literature it was found L_1 fracture was the highest (53.33%) site of fracture[13].

In present study it was found that the 45.00% of sufferer had L_1 fracture. The second highest was D_{12} fracture (25.00%). Present study showed 90.00% of patient had parapares, 10.00% had manoparesis and 50.00% patient had bladder dysfunction. Others had bowel and sex dysfunction. Fusion done with autologus bone graft from iliac crest. Fixation was done with titanium Z plate & screw in cases of 85.00% of patients.

In case of 15.00% patients fixation was done with titanium cages & bone chips. It was revealed that excellent improvement occurred in 8(40%) cases, good recovery occurred in 9(45%) cases, fair recovery occurred in 1(5%) cases and 2(10%) had poor outcome. Among the autonomic dysfunction, bladder function improved in 6(60%) cases, bladder and bowel function improved in 1(33.33%) case and sexual dysfunction improved in 1(50%) case. Among the 20 cases 18(90%) patients had sensory dysfunction. After surgery in 16(88.89%) cases sensory dysfunction improves.

Keneda et al, reported 64.00% of their patients had excellent and 28.00% had good outcomes, 6.00% showing fair and 2.00% demonstrats poor outcome[14].

Three (15%) had wound infection, which was treated by antibiotic therapy after wound swab culture & dressing. The 05.00% of patients had one screw displacement. But the patient was stable.

One (05.00%) of patient had excessive peroperative bleeding by injury of lumbar vessels & treated by ligation of vessels and 05.00% of patient another had respiratory distress with pulmonary oedema and pneumonia which was managed by O_2 therapy, proper antibiotic, morphine & frusemide injection. There was no mortality.

Conclusion:

Patient with incomplete spinal cord injury showed good to excellent recovery and could be mobilized early with external support by anterolateral retroperitoneal approach with Z plate fixation.

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Intracranial Aneurysms: Acute VS Delayed Surgery - An Analysis of 52 Cases

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Abstract:

Background: *Aneurysm surgery is increasing day by day in our country but the exact timing of surgery is still controversial.* ***Objectives:*** *The aim of this study was to determine the results of early and late surgery for aneurismal subarachnoid haemorrhage. The aim of microneurosurgical management of an aneurysm is the total occlusion of the aneurysm sac by clipping at the neck of aneurysm with preservation of flow in the parent artery and preservation of all its perforating arteries with minimal or no brain retraction.* ***Methods:*** *There were 52 patients included in this study among them 3 patients expired soon after the admission before surgery could take place. Hence 49 patients underwent clip surgery from July 2005 to May 2012 for 52 aneurysms because 3 patients harboured multiple aneurysms. Patient's history, clinical findings, Hunt & Hess grading, Fisher grading of CT scan, preoperative & postoperative CT angiography, postoperative outcome were collected and analyzed.* ***Results:*** *Most of the clipping (57.14%) were done in intermediate stage (4th to 10th days), because patients usually referred from peripheral hospital on 2nd or 3rd day after the acute SAH Those who was admitted early and H&H status good, was fit to do early surgery (within 3rd day), (28.57%). Overall outcome was assessed at 3 months after SAH using the Glasgow Outcome Scale. Good outcome were observed in 40 cases among them 22 cases (42.3%) were able to return premorbid activities. Total mortality in this series were 10 cases (19.23%) which includes preoperative death while waiting for clipping -3 cases and postoperative death- 7 cases(14.2%).* ***Conclusion****: There is no reason to postpone clipping surgery in patients who are eligible for surgery at day 5. Surgery after day 10 is associated with worse outcome. Although these studies is having high rate of mortality which can be progressively minimize by our continuous improvement of surgical skills and postoperative critical care management of aneurysm patients.*

Key word: *aneurysm, craniotomy, clipping.*

Introduction:

Aneurysms resemble bubbles or focal dilation of arteries that occur at weak points of the artery wall (figure-1). There are many factors for its formation. These factors include genetic predisposition, the anatomy of the artery and its branches, 'wear-and-tear' on the wall of the arteries due to blood flow, artery disease and cigarette smoking[1]. Aneurysms are the most common at circle of Willis in the central skull base. Approximately 80% of aneurysms arises from anterior circulation of the brain, while 20% form posterior circulation of the brain[1.2].

It is uncommon to diagnose an aneurysm before it has ruptured and most people with aneurysms are unaware that they have an aneurysm until it bursts. Overall 3.6-6% of normal population has aneurysm, among them 1.4-1.9 % rupture in a year. Women have more tendencies to rupture. There is seasonal variation of rupture[3].

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It is known that the majority of aneurysms that have ruptured are less than 10 mm in size[3,4]. Over the next 5 years after diagnosis an average aneurysm between 2 and 6 mm in size has a risk of bleeding between 1 and 2%, an aneurysm between 7 and 9 mm size has a five year risk of bleeding of 6%, an aneurysm between 10 and 24 mm in size has a five year risk of bleeding of 11% and larger aneurysms have a 28% chance of bleeding[3,4].

The history of intracranial aneurysm surgery is not a long one. The first direct operation on an intracranial aneurysm was performed by Norman Dott, who wrapped a ruptured aneurysm in 1933, and the first clipping of an aneurysm was performed by Walter Dandy in 1938[5,6]. The results of surgery improved dramatically when the operating microscope was introduced in the 1960s and a subsequent improvement followed the use of the calcium antagonist nimodipine and the maintenance of a high fluid intake to lessen the risk of delayed cerebral ischemia[7]. For many years clipping for the aneurysm was regarded as the definitive mode of treatment, but the development of the GDC coil in 1990 allowed an alternative approach that avoided the hazards of open surgery[7].

After an aneurismal subarachnoid haemorrhage, there are two major sources of morbidity and mortality: rebleeding and delayed ischemia secondary to cerebral vasospasm. The incidence of rebleeding is greatest immediately after the initial haemorrhage, and the incidence of vasospasm is highest between the 5th and 9th days after the ictus[8]. It thus seems logical to proceed with early surgery, such an approach is certainly the best means for eliminating rebleeding as a source of morbidity and mortality. Early surgery also facilitates the management of cerebral vasospasm by volume expansion and induced hypertension manoeuvres that are quite risky in the patient with an untreated aneurysm[8].

The anterior communicating artery (AcomA) is a recognized site of aneurysm predilection accounting for more than one fourth of all cerebral aneurysms in several large studies[9]. Because of

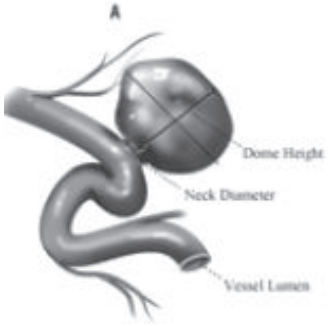


Fig.-1: *Showing various dimensions of an aneurysm*

the complexity and diversity of the geometry and flow conditions in the AcomA, it is not surprising that aneurysms of the AcomA are considered the most complex of the anterior circulation. It is widely believed that the initiation, growth, and, ultimately rupture of cerebral aneurysms are related to the interaction between hemodynamic forces with the arterial wall biology, resulting in a localized weakening of the wall. Aneurysms of the AcomA complex are more likely to have asymmetric A1 segments and furthermore, to have exclusive filling angiographically from A1 segment in up to 78% cases.[9]

Posterior communicating artery (PCOM) aneurysms are another most common aneurysms encountered by neurosurgeons and neuro-interventional radiologists and are the second most common aneurysms overall (25% of all aneurysms) representing 50% of all internal carotid artery (ICA) aneurysms[10]. Not only these aneurysms can present with a typical subarachnoid haemorrhage, but also they can present with an isolated oculomotor nerve palsy (OMNP) or a non-traumatic subdural hematoma (SDH).

Jane *et al*, evaluated the risk of rehaemorrhage in ruptured ACOM and PCOM aneurysm, finding a 50% risk of rerupture within the initial six months followed by 3.5% per year thereafter[11].

The surgical treatment of basilar tip aneurysms remains one of the most difficult tasks in neurosurgery because the view is obscured due to the depth of the aneurysm, overlapping neurovascular and bony structures, and the proximity of perforators[12].

Despite the many studies about timing for surgery in subarachnoid haemorrhage (SAH), the optimum time is still in debate. The aim of this study was to determine the results of early and late surgery for aneurysmal subarachnoid haemorrhage. The proponents of early surgery focused on reduction of the devastating effects of aneurysmal re-bleeding within the first 2 weeks and its high mortality. On the other hand, some authors believe that delayed surgery may be better choice, because operating on the acutely injured brain may be associated with high risk for surgical morbidity and mortality[13].

Some studies advocates surgery neither early nor late, and indicate that the intermediate period in 4 to 10 days after the SAH is a risky time for surgery, because during this period the risk for cerebral vasospasm and ischemia may be very high[14].

Unlike the authors, it is our belief that early aneurysm surgery is a technically more challenging procedure than delayed surgery. Despite the use of osmotic agents, hyperventilation, and cerebrospinal fluid drainage, it is our opinion that the brain is more friable and difficult to retract safely.

However, Shabepour *et al.* study in Iran had some results different from most previous studies; they evaluated 110 aneurysmal SAH and reported that the complications of late surgeries were significantly lower than early surgeries; the complication rate in surgeries performed during first 3 days after SAH was 66.7%. This rate was 54.57% for surgeries in 3 to 14 days after SAH, and 22.9% for surgeries after 14th days[15].

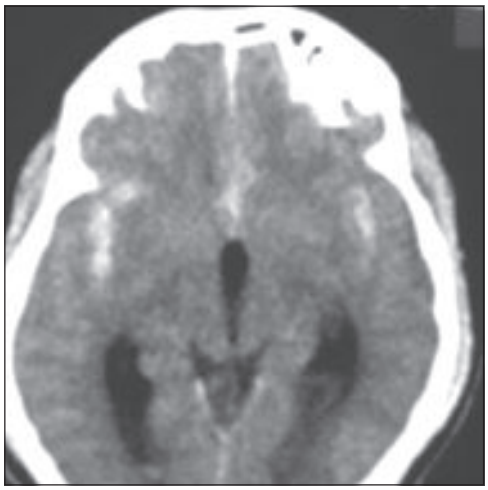


Fig.-2: *CT scan shows of SAH, Fisher grade 2.*

The aim of microneurosurgical management of an aneurysm is the total occlusion of the aneurysm sac by clipping at the neck of aneurysm with preservation of flow in the parent artery and preservation of all its perforating arteries with minimal or no brain retraction.

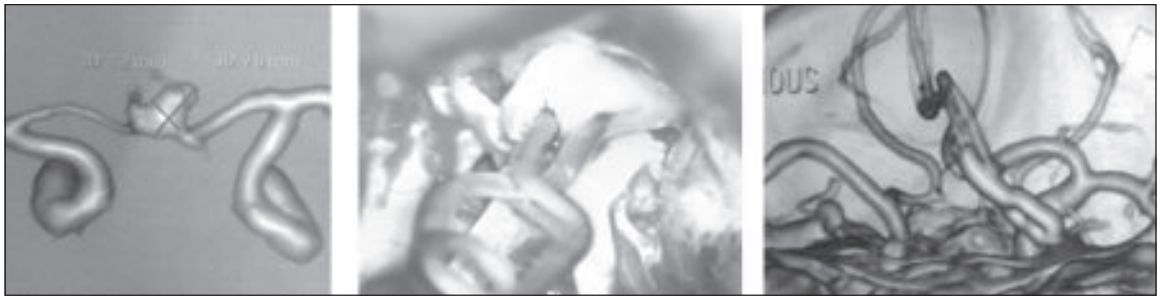
Methods:

There were 52 patients included in this study among them 3 patients expired soon after the admission before surgery could take place. Hence 49 patients underwent clip surgery from July 2005 to May 2012 for 52 aneurysms because 3 patients harbored multiple aneurysms. Patients' history, clinical findings, Hunt & Hess grading, Fisher grading of CT scan (figure-2), preoperative & postoperative CT angiography, postoperative outcome were collected and analyzed.

About 90% of aneurysms were accessible via a standard frontotemporal (pterional) craniotomy centered over the pterion. Only occasional cases, aneurysms of the distal anterior cerebral artery and the lower vertebrobasilar trunk, require different surgical approaches. The risk of intraoperative rupture of the aneurysm, which occurs in 5-10% of cases, can be minimized by induction of hypotension. This seems a safe measure provided that the anaesthetist ensures maintenance of a high blood volume. We preferred not to apply temporary clips to the main artery proximal to the aneurysm because it was associated with a high incidence of ischemic cerebral damage. Temporary clipping was certainly not tolerated if the blood pressure is lowered at the same time.

Surgical steps

Acom aneurysm: Pterional craniotomy is commonly done for this. We prefer to approach from right side however sometimes it needed to approach from left side when. Left A1 is dominant and Ipsilateral and contralateral A2 is well visualized from left side. We prefer 5-10 degree rotation to the contralateral side to keep the figure of H in vertical position. Wide sylvian fissure dissection was done for gentle retraction of frontal lobe. Anterior interhemispheric fissure was dissected to avoid gyrus rectus resection (figure-3A,3B,3C).



A B C

Figure-3: *CT angiogram shows ACOM aneurysm (A), Peroperative clipping of ACOM aneurysm (B) & Post clip angiogram shows no residual aneurysm (C).*

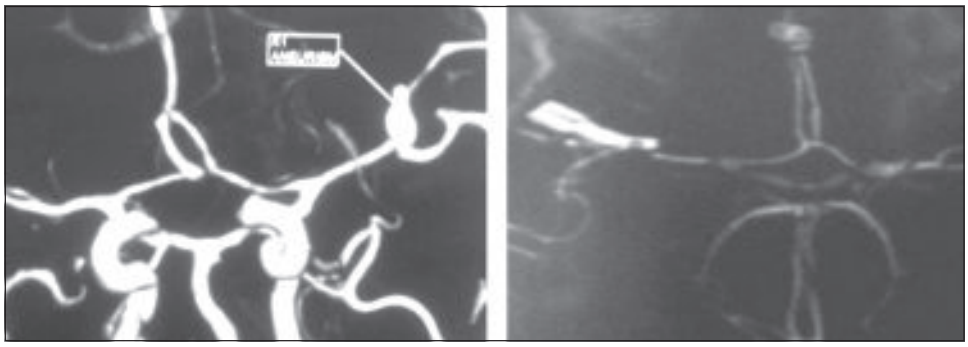
Pcom aneurysm: Pterional craniotomy with rotation 60-75 degree to contralateral side for posteriorly directing aneurysm which allows the aneurysm to be seen in profile with carotid artery. The oculomotor nerve should be identified and protected. It is not necessary to expose the aneurysm dome. When the inferior and superior aspect of aneurysm has been identified and adjacent arteries made free, then the aneurysm can be safely clipped.

MCA aneurysm: Pterional approach with turning the patient head 45 degrees to contralateral side - means the operative pathway will be almost vertically downward along the sphenoid ridge. This reduces the need for retraction of temporal lobe , and often only needs the frontal lobe to be retracted. The head is also extended to allow the frontal lobe to fall. Finally the rotated, extended head is elevated upward to facilitate venous return.

Basilar top aneurysm:

Pterional craniotomy with head is positioned in a Mayfield head holder with the head elevated above the shoulder level and 20 dergree rotation to the contralateral side away from the operative side. The head is extended until the maxillary eminence is highest point in the field. A pterional craniotomy is then performed followed by drilling of sphenoid ridge and orbital roof until a flat surface is achieved so that straight trajectory to the proximal carotid can be visualized along the skull base.

For preexisting hydrocephalus or in case of brain swelling during surgery we are in need of brain relaxation. This can be done by a ventricular catheter placed in “paine’s point”. This is done by aiming perpendicularly to the triangle 2.5 cm back along the sylvian fissure and 2.5 cm superiorly.



A B

Figure 4: *CT angiogram shows left MCA aneurysm (A) & Post-clip angiogram shows no residual aneurysm (B).*

Results:

The mean age group of our study was 45.7 years. Age varies from 16- 70 years. Male: female ratio was 1:08. In our study male are commoner then female.

Hunt and Hess grades at admission are summarized in Table I. Thirty seven patients (71.2%) were classified as Grade I-II, Twelve patients (23.0%) as Grade III-IV. 3 patients (5.7%) as Grade V.

Table-I

Distribution of Hunt & Hess Grading: (n=52)

Hunt & Hess Grading	No. of cases
I – II	37 (71.215%)
III-IV	12 (23.07%)
V	3 (5.76%)

The subarachnoid clot thickness -Fisher grading at admission were summarized in Table-II. 84.4% of cases were in grade I-II. 4 cases(7.6%) were in grade III-IV. Only 4 cases (7.6%) were grade V.

Table-II

Distribution of Fisher grade of Aneurysms: (n=52)

Fisher Grading	No. of cases
I – II	44 (84.61%)
III-IV	4 (7.69%)
V	4 (7.69%)

Cerebral CT angiography was performed at admission in all patients (angiography was performed within 48 hours of haemorrhage onset in most of the cases). The location and size of the ruptured aneurysm were obtained from a review of angiographic images. Commonest aneurysm found in ACOM location which was 42.30%. Next commoner the PCOM which constitute 26.92% and MCA aneurysms were 9.61% . Basilar top aneurysms were found only in 4 cases (7.6%) (Table-III). The aneurysm was single in 92.9% and multiple aneurysms were found in 3 cases (5.76%).

Table-III

Distribution of CT angiographic findings of Location of Aneurysms:(n=52).

Location of Aneurysms	No. of aneurysms
ACOM aneurysm	22 (42.30%)
PCOM aneurysm	14 (26.92%)
MCA aneurysm	5 (9.61%)
ICA aneurysm	5 (9.61%)
DACA aneurysm	2 (3.84%)
Basilar top aneurysm	4 (7.69%)
Paraclinoid aneurysm	2(1.92%)
Vertibrobasilar junctional aneurysm	1(1.92%)
Total	52 (100%)

Aneurysm size was categorized in three groups. Small sizes were between 4-10 mm - constitute the commonest size which were 84.6%. Large sizes were between 11-25 mm constitute 11.5% and >25 mm were giant aneurysm which was only2 cases(Table IV).

Table-IV

Distribution of Size of Aneurysms, (n=52)

Size of Aneurysms	No. of Aneurysms
4mm – 10mm	44 (84.61%)
11mm – 25mm	6 (11.53%)
<25mm	2 (3.84%)
Total	52

Pterional craniotomy (91.8%) was the most common approach for most of the aneurysm both for almost all anterior and some posterior circulation aneurysm. Contralateral pterional approach were done in 3 cases(6.12%). For vertebrobasilar junction retrosigmoid suboccipital craniectomy was choiced. For DACA aneurysm anterior interhemispheric approach was chosed.(Table-V).

Table-V

Distribution of Name of Surgery (n=49)

Name of Surgery	No. of cases
Pterional Crainotomy	45 (91.83%)
Orbitopterional Crainotomy	1 (2.04%)
Contralateral Pterional Crainotomy	3 (6.12%)
Retrosigmoid suboccipital approach	1(2.04%)
Total	49 (100%)

Most of the surgery(57.14%) were done in intermediate stage(4^{th} to 10^{th} days), because

patients usually referred from peripheral hospital on 2nd or 3rd days after the acute SAH. Those who was admitted early and H&H status good , was fit to do early surgery (within 3rd day) (28.57%). Those who were poor H&H grade at admission and or CT angiogram reveled sign of vasospasm and those having medical co-morbidity such as asthma, coronary ischemia, were not able to do early or intermediate surgery hence they were selected for late surgery(after 11th day onward)(table-VI). Two patients who died from rebleeding while waiting for surgery although they were fit for surgery at anytime. Another one patients died from severe vasospasm so soon after admission that surgery could not have been performed.

Table-VI

Distribution of Day of Aneurysm Surgery (n=49)

Day of Aneurysm Surgery	No. of aneurysms
1st day – 3rd day	14 (28.57%)
4th – 10th day	28 (57.14%)
>11th day	7 (14.28%)
Total	49 (100%)

Overall outcome was assessed at 3 months after SAH using the Glasgow Outcome Scale. Good outcome were observed in 40 cases among them 22 cases (42.3%) were able to return premorbid activities. Poor outcome was defined by the Glasgow Outcome Scale criteria of death, vegetative state, or severe disability. Total mortality in this series were 10 cases (19.23%) which includes preoperative death while waiting for clipping -3 cases and postoperative death -7 cases(14.2%) (Table -VII).

Table-VII

Distribution of Glasgow outcome scale (N=52)

Good outcome	No. of cases
1. Return to premorbid occupation	22(42.30%)
2. Neurologically normal, not returned to premorbid occupation	10(19.23%)
3. Independent, mild neurological deficit	5(9.61%)
Poor outcome	
4. Dependent, significant deficit	5(9.61%)
5. Dead(preop-3cases + (14.2%) postop-7cases	10(19.23%)
Total	52 (100%)

Commonest complication of aneurysm sugery were rerupture during dissection of aneurysm sac which occurred 7.6% cases. Incompletely clipped aneurysm also reruptured in postoperative period which occurred 3.8% cases. Postoperative severe hypotension developed in 5.7% cases. Most common causes of postoperative mortality in our series were from hypotension and improper management of vasospasm. Rerupture from incompletely clipped aneurysm were accounted 2 cases which lead to death(table-8). Postoperative vasospasm & limb weakness were another common problem for which we need to manage by ionotrophic agent like dopamine, adrenaline & dobutamine. Subdural hematoma , meningitis , and acute and late hydrocephalus were some minor complications (Table- VIII).

Table-VIII

Distribution of Complications of Aneurysm (n=52)

Complication	No. of cases
Re-rupture while waiting	2 (3.84%)
Preop severe vasospasm	1(1.92%)
Intraoperative rupture	4 (7.69%)
Post operative rupture	2 (3.84%)
Post operative hypotension	3 (5.76%)
Pre operative vasospasm	6 (11.53%)
Newly developed Post operative vasospasm & hemiplegia	5 (9.61%)
Post operative subdural haematoma	2 (3.84%)
Meningitis	5 (9.61%)
Hydrocepalus	3 (5.76%)
Tension pneumocephalus	1(1.92%)
VP shunt	3 (5.76%)
No complications	15(28.84%)
Total	52(100%)

Discussion:

Pterional craniotomy was the most common approach for both anterior and posterior circulation aneurysm[16]. However some author choose orbitopterional craniotomy in case of ACOM aneurysm in acute setting. In one study overall outcomes at discharge using the Glasgow outcome scale of those who underwent pterional craniotomy were good in 52 (69.4%) patients, fair in 13

(17.3%), and poor in 10 (13.3%) among 75 cases of ACOM aneurysm. At last follow-up after 6 months of surgery, outcomes were good in 63 (84%) patients, fair in 6 (8%), and poor in 6 (8%). Disability included mild in 10%, partial in 18.8%, moderate in 8.6%, moderately severe in 1.4%, severe in 2.9%, extremely severe in 2.9%, and vegetative state in 1.4%. Overall 74% of patients returned to work after 4 months, 83% of previously unemployed patients returned to baseline, and 25% were disabled[17]. In this study good outcome were observed in 40 cases among them 22 cases (42.3%) were able to return premorbid activities. Poor outcome were observed in 15 cases among them 7 cases were died following surgery(14.2%) Here our postoperative mortality was quite high (14.2%), this was probably from interaction of many factors –such as patient factor-delay admission, hesitation regarding giving consent for operation in good H&H status, postoperative poor nursing management , and surgeons skill.

Samson *et al.* reported that the outcome and complications of early surgery on first 8 days after SAH were not different from late surgery in 9 to 31days after SAH, but ischemic events after early surgery were significantly higher[18].

Temporary clipping and projection of the aneurysm did not affect the outcome. Causative factors of unfavorable outcomes were primary brain damage by haemorrhage in cases of small and large aneurysms and perforator damage in the case of giant aneurysm. Poor clinical H&H grade and vasospasm are the causative factors of poor outcome in patients with ruptured aneurysm. The poor outcome could also have been correlated with poor clinical condition at admission, early rebleeding , or early deterioration from other causes[19].

Once the neck of the aneurysm was adequately exposed, then we must pay significant attention to preservation of the parent artery, perforators without significant manipulation of the fundus[19]. Leipzig *et al*, reviewed a large series of aneurysm clipping looking for risk factors of intraoperative rupture. PCOM aneurysms had the second highest rate of intra-operative rupture (second only to ACOM aneurysms) amongst anterior circulation aneurysms[20] .

A strong correlation was found between rehaemorrhage and residual aneurysm. Risk of rehaemorrhage increased from 1.1% in completely occluded aneurysm to 17.6% in a partially treated aneurysm where residual filling of the dome was left untreated. Also the median time to rerupture was only three days[19]. In our series 2 cases developed reruptured in early postoperative period among 49 cases of operatively treated aneurysm (table-VIII)

Aneurysm surgery are increasing day by day, probably because of improvement of motivation of the patient party, availability of investigation and availability of aneurysm clip of various size and shape in our country.(Diagram-1)

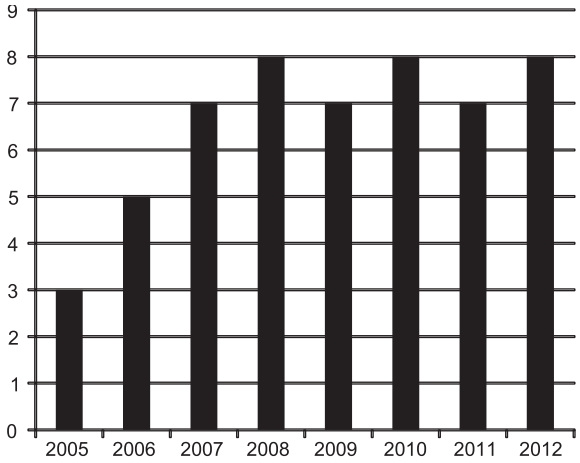


Diagram-I *Bar diagram of aneurysm cases in year. (n=52).*

There are 3 possible explanations for the observed better outcomes among SAH patients treated within 72 hours of admission: (1) the death and disability associated with rebleeding is reduced; (2) the death and disability related to cerebral vasospasm is reduced because more intensive measures can be undertaken with secured aneurysms; and (3) early treatment is a marker of higher performance on several quality care parameters [20].

The international cooperative study on the timing of aneurysm surgery recruited 3521 patients with aneurusmal SAH. There was no difference in good

outcome defined by Glasgow outcome scale at 6 months in early (0-3day) and delayed (11-14 day) surgery group but lower rate were observed in intermediate (7-10 day) surgery group. The rate of rebleeding in early surgery group 5.7% in compared with 13.9% delayed surgery group[21]. A subgroup analysis on north American population(772 patients) demonstrates high rate of good outcome in early vs delayed group (70.9%-61.7%) respectively even though there is no mortality. A recent data reevaluate the definition of early treatment (0-2 days vs 0-3 days) proposed by international cooperative study trail. A major benefit of early surgery lies in the decreasing frequency of rebleeds that occurs in the interim period before aneurysm treatment is performed[22].

In our study the hospital stay in early surgery group was significantly lower than late group. This finding is concordant with Ross *et al.* [23] and Bolander *et al.* studies[24].

Conclusion:

In conclusion, this study revealed that most of the aneurysm surgery were done between 4th to 10th days of post acute SAH, which reflects that timing of surgery should be individualized for each patient based on clinical situation such as age, H&H Grading, Fisher Grading, size and site of aneurysm, presence or absence of vasospasm and other medical comorbid factors. There is no reason to postpone clipping surgery in patients who are eligible for surgery at day 5. Surgery after day 10 is associated with worse outcome. Although this study is having high rate of mortality which can be progressively minimize by our continuous improvement of surgical skills and postoperative critical care management of aneurysm patients.

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MRI of Diffusely Infiltrating Intracranial Astrocytomas: Association between the Volume of Peritumoural Edema and the degree of Contrast Enhancement

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Abstract:

Background: *The development of peritumoural edema and contrast enhancement of brain tumour is both thought to be due to breakdown of blood-brain barrier. However, the exact mechanisms by which these phenomena occur are not completely understood. Our purpose was to find association between the volume of peritumoural edema and the degree of contrast enhancement in MRI of diffusely infiltrating astrocytomas.* ***Method:*** *A total of 42 patients with intracranial astrocytomas diagnosed by MRI findings who underwent surgery with histopathology showing diffusely infiltrating astrocytomas were selected from the study population. The volume of peritumoural edema was measured and visual assessment of the degree of contrast enhancement was scored.* ***Result:*** *A highly significant association was found ($p<0.001$) between the volume of peritumoural edema and the degree of contrast enhancement.* ***Conclusion:*** *These results can be viewed as indirect, radiological evidence that edema production is quantitatively related to the degree of breakdown of the BBB as determined by the gadolinium enhancement.*

KEY WORDS: *Astrocytoma, Peritumoural edema, Degree of contrast enhancement*

Abriviation: *BBB (Blood brain barrier), CT (Computary tomography), MRI (Megneting resonance imaging).*

Introduction:

Brain edema associated with brain tumour is one of the most important factor contributing to the morbidity and mortality associated with brain tumour. The major mechanism for edema formation within and around brain tumour is abnormal permeability of newly created microvessels in the growing tumour. It was found that endothelial proliferation is common in malignant gliomas and that new tumour vessels are derived from previously existing vessels. However, these newly formed vessels are often defective. These defective vessels form an ineffective barrier and allow leakage of plasma exudates into the surrounding brain[1]. It is thought that enhancement of brain tumour by contrast media in CT and MRI is due to open interendothelial junctions, fenestrae, gap junctions and increased pinocytic vesicles in the capillaries of these tumours[2]. However, it is not known whether the putative defect, which governs the development of edema, is the same as one, which causes contrast enhancement. It is also not known whether these two factors are related to each other or how they are related to the degree of damage to the BBB. The present study is aimed finding association between the volume of peritumoural edema and the degree of contrast enhancement in MRI of diffusely infiltrating astrocytomas.

Material and methods:

This study was carried out at the Department of Neurosurgery, Bangabandhu Sheikh Mujib Medical

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University, Dhaka, during the period from July 2006 to April 2008. All admitted patients with intracranial astrocytomas who underwent surgery were considered as a study population. A total of 42 patients with intracranial astrocytomas diagnosed by MRI findings who underwent surgery with histopathology showing diffusely infiltrating astrocytomas were selected from the study population.

The volume of tumour and edema was measured by modified ellipsoid formula simply by p/6´ABC which practically amounts to 1/2´ABC where A= Largest anterior- posterior length in centimeter, B= Largest width in centimeter, C= Largest vertical length in centimeter. To measure volume of edema initially both tumour and edema volume was calculated as a unit, then the tumour volume was subtracted from the total (Fig. 1).

Visual evaluation of the degree of contrast enhancement was scored on 0-2 scale, with 0 = no enhancement (Fig. 2), 1 = equivocal enhancement (Fig. 3) and 2 = definite enhancement[3] (Fig. 4).

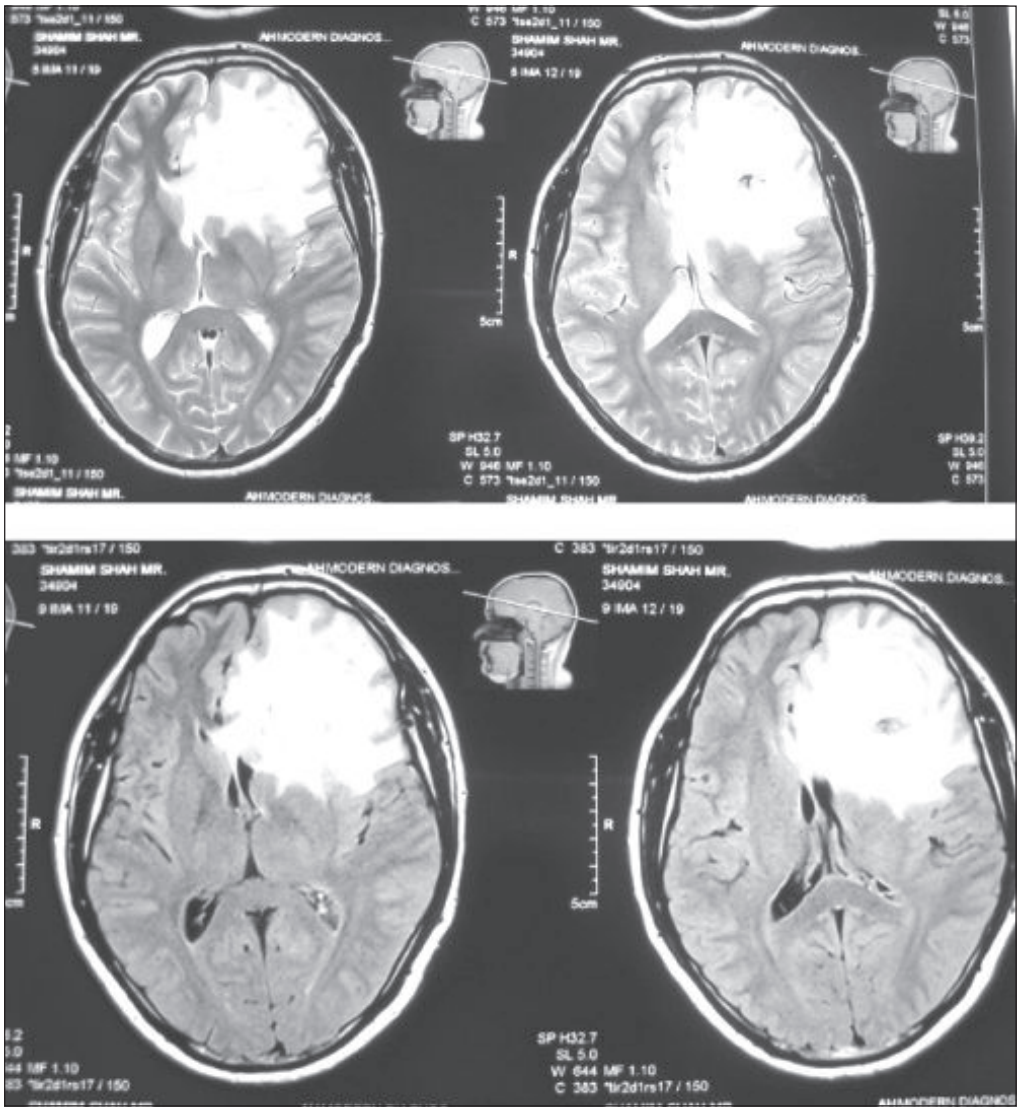

Fig.-1: *MRI of GBM, T2 weighted image& Flair showing peritumoural edema.*

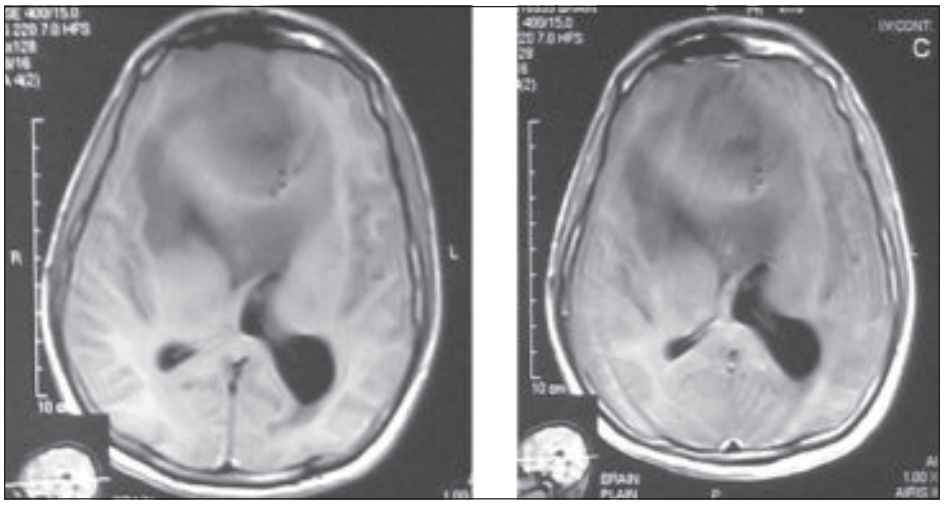

Fig.-2: *MRI of low grade glioma, T1 weighted image Pre & Post-contrast. Degree of contrast enhancement: None.*

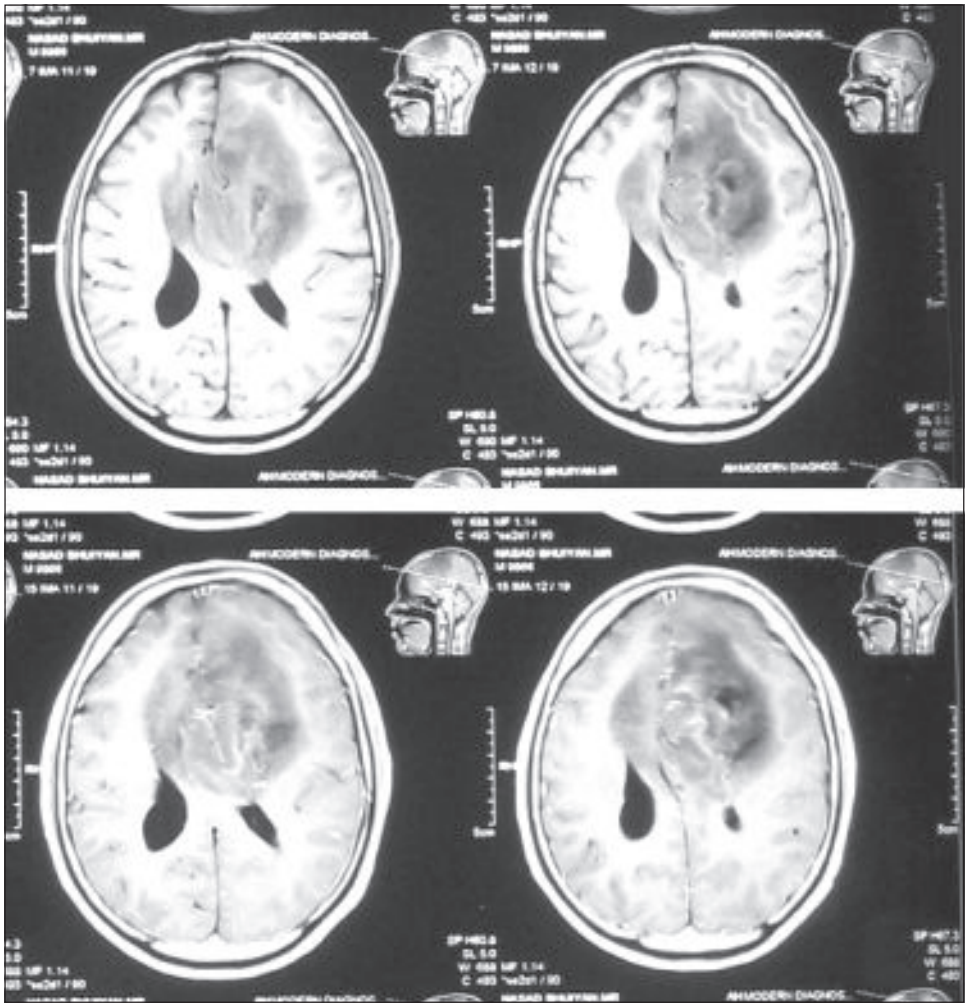

Fig.-3: *MRI of Low grade glioma, T1 weighted image Pre & Post-contrast. Degree of contrat enhancement: Equivocal.*

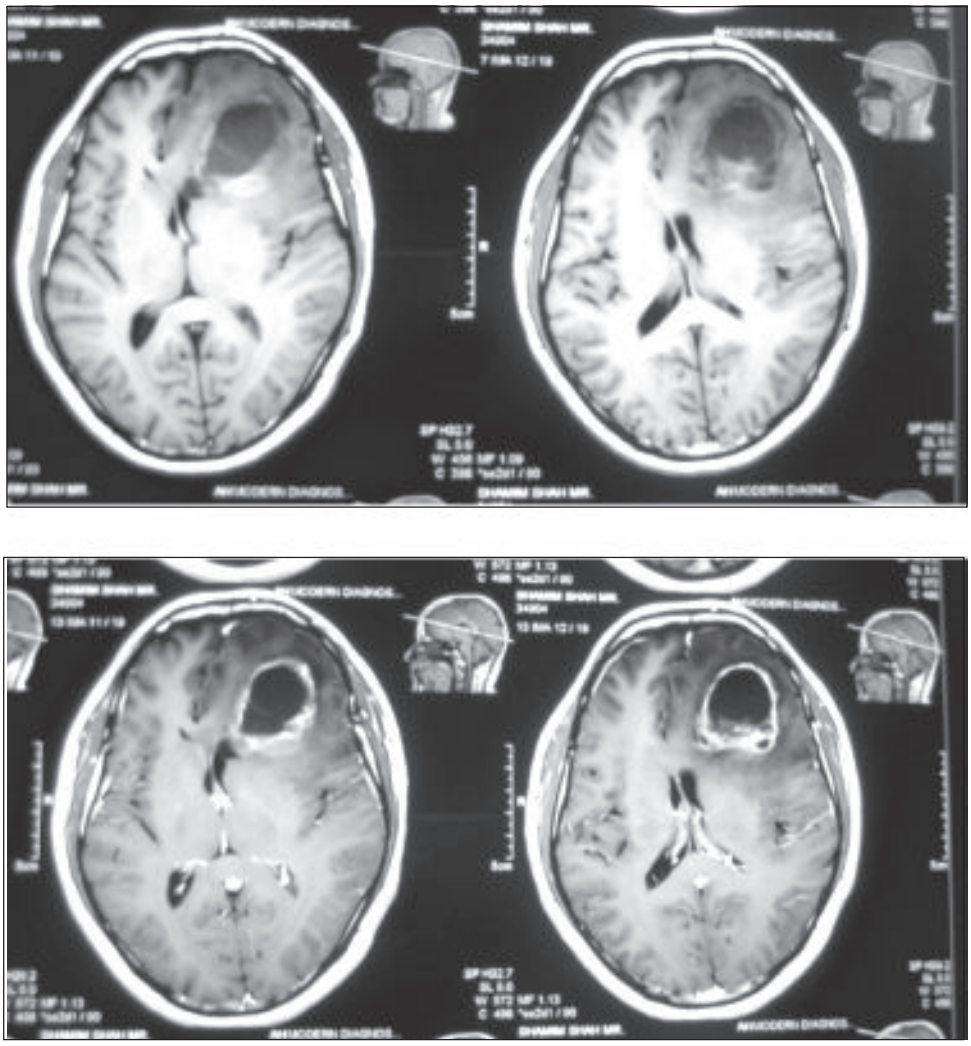

Fig.-4: *MRI of GBM, T1 weighted image Pre & Post-contrast. Degree of contrast enhancement: definite.*

Results:

A total of 42 cases of diffusely infiltrating astrocytomas diagnosed by MRI and cofirmed by histopathological report were taken as study sample. The age distribution of 42 patients ranged from 8 – 60 years. The mean ± SD age was 36.6 ± 14.28. The peak age incidence was 31 –40 age group (Table I). A male preponderance was observed among the admitted cases with male to female ratio was 2.5:1. In this study, out of 42 patients of intracranial astrocytomas, regarding location of the tumour, maximum 29(69%) patients had hemispheric lesions. 6(14.3%) patients had cerebellar lesion, 6(14.3%) patients had diencephalic lesion and 1(2.4%) patient had brainstem lesion (Table II). Regarding the volume of tumour maximum patients 21 (50%) had tumour volume of <25 cc. The range of tumour volume was 2 – 224 cc. The range of peritumoural edema volume was 0 – 137 cc. Maximum 21 patients had edema volume >50 cc (Table III). Most of the astrocytoma's showed definite degree of contrast enhancement i.e. 31 (73.8%) with 6 (14.6%) having no contrast enhancement and 5 (11.9%) having equivocal degree of contrast enhancement (Table IV). Histopathologically 26.2% was grade II astrocytoma, 21.4% was grade III astrocytoma and 52.4% were grade IV astrocytoma (Table V).

Association between the volume of peritumoural edema and the degree of contrast enhancement

was found significant (p <0.001) in 95% confidence limit (Table VI). More the volume of peritumoural edema, more was the degree of contrast enhancement. The study demonstrated significant association (p<0.001) between volume of peritumoural edema and histological subtype in patients with diffusely infiltrating astrocytomas (Table VII). The present study also showed significant correlation (p<0.001) between the degree of contrast enhancement and histopathological subtype of tumour (Table VIII).

Table-I

Age distribution of patients with Astrocytomas

Age group in year	Frequency	Percent
<10	2	4.8
11-20	4	9.5
21-30	9	21.4
31- 40	11	26.2
41- 50	10	23.8
>50	G	14.3
Total	42	100

Table-II

Location of tumour in patients with diffusely infiltrating astrocytomas

Location of tumour	Frequency	Percentage
Hemispheric	29	69
Cerebellar	6	14.3
Diencephalic	6	14.3
Bramstem	1	2.4
Total	42	100

Table-III

Volume of peritumoural edema in patients with astrocytoma

Edema volume (cc)	Frequency	Percentage
25	13	31
25-50	8	19
50	21	50
Total	42	100

Table-IV

Degree of contrast enhancement in patients with astrocytoma

Degree of contrast enhancement	Frequency	Percent
None	6	14.6
Equivocal	5	11.9
Definite	31	73.8
Total	42	100

Table-V

Histopathological subtypes in patients with astrocytoma

Histopathology	Frequency	Percentage
Low grade astrocytoma	11	26.2
Anaplastic astrocytoma	9	21.4
Glioblastoma multiformae	22	52.4
Total	42	100

Table-VI

Association between the volume of peritumoural edema and the degree of contrast enhancement

Degree of contrast enhancement	Volume of peritumoural edema (cc)				χ^2 value	p value
	<25	25-50	>50	Total		
None	6	0	0	6	26.46	<0.001
Equivocal	4	1	0	5		
Definite	3	7	21	31		
Total	13	8	21	42		

Table-VII

Association between the volume of peritumoural edema and the hitopathological subtype of tumour

Histo-pathological subtype	Volume of peritumoural edema (cc)				χ^2 value	p value
	<25	25-50	>50	Total		
Low grade astocytoma	9	2	0	11	22.95	<0.001
Anaplastic astrocytoma	2	3	4	9		
Glioblastoma multiforme	2	3	17	22		
Total	13	8	21	42		

Table-VIII

Association between the degree of contrast enhancement and the hitopathological subtype of astrocytomas

Histo-pathological subtype	Degree of contrast enhancement				χ^2 value	p value
	None	Equivocal	Definite	Total		
Low grade astocytoma	5	5	1	11	33.34	<0.001
Anaplastic astrocytoma	1	0	8	9		
Glioblastoma multiforme	0	0	22	22		
Total	6	5	31	42		

Discussion:

The question of peritumoural edema remains pivotal for the clinical management of the patients with astrocytomas. Understanding brain edema is crucial to the effective treatment of tumours. The present study was conducted at the department of Neurosurgery, BSMMU, Dhaka during the period of July 2006 to April 2008 to find the association between the volume of peritumoural edema and the degree of contrast enhancement as seen in MRI of diffusely infiltrating astrocytomas. The final study subjects were 42 patients with diffusely infiltrating astrocytomas. The age ranged from 8 years to 60 years. Mean age was 36.6 years. The highest incidence was in between 31- 40 years. Age incidence in diffusely infiltrating astrocytomas is an important variable, which is observed to vary from study to study. In present study, no particular age was found susceptible to develop astrocytoma, although more than one third (38%) of the study cases were the age of 40 years or above. The mean age was found to be 36.6 years which is almost consistent with the findings of other series[4,5]. Variation of astrocytomas with respect to sex is not also uncommon. Astrocytomas are more common in males (M:F = 3:1)[6]. In our study we found a male predominance at the ratio of 2.5:1 bearing consistency with findings of other investigators[4].

In the present study regarding the location of tumour, hemispheric lesions were commonest (69%) followed by cerebellar and diencephalic lesions (14.3%). The brainstem variety was least common (2.4%). In adult cases hemispheric astrocytomas were common while cerebellar lesions were more common in children[6]. This was not observed in the present study probably due to the fact that pilocytic astrocytoma,one of the more common pediatric brain tumour was not included in the study.

In this study, regarding peritumoural edema volume, maximum 21 patients had edema volume >50 cc. The Mean ± SE of peritumoural edema volume was 56.36 ± 6.76 cc. The range of peritumoural edema volume was 0 – 137 cc.

In the present study regarding degree of contrast enhancement, 6 (14.6%) patients showed no enhancement, 5 (11.9%) patients showed equivocal enhancement and 31 (73.8%) patients showed definite enhancement after administration of contrast agent. Association between the volume of peritumoural edema and the degree of contrast enhancement was found significant ($p < 0.001$) in 95% confidence limit. More the volume of peritumoural edema more was the degree of contrast enhancement. The findings offer indirect radiological evidence that the defect in the BBB which causes edema is etiologically related to the defect in BBB responsible for contrast enhancement[7]. Significant correlation can be found ($p=0.0006$) between the volume of peritumoural edema and the degree of contrast enhancement in gliomas[8].

In our study regarding histopathological diagnosis, 26.2% was grade II astrocytoma, 21.4% was grade III astrocytoma and 52.4% were grade IV astrocytoma. In diffuse fibrillary astrocytomas there is direct correlation between peritumoural edema with tumour grade ($p<0.01$)[9]. Our study also demonstrated significant association ($p<0.001$) between volume of peritumoural edema and histological subtype in patients with diffusely infiltrating astrocytomas.

The present study also showed significant correlation between the degree of contrast enhancement and histopathological subtype of tumour ($p<0.001$). This was also found in another study[10]. It was also found that there is direct relationship between contrast enhancement and

neovascularity present in high grade tumours[11]. However, in low-grade astrocytomas with little or no alteration of BBB, contrast agent did not enter the extravascular space and no significant contrast enhancement was observed[12].

Conclusion:

In our study we have found that there is significant association between the volume of peritumoural edema and the degree of contrast enhancement in MRI of diffusely infiltrating intracranial astrocytomas. Thus the finding of the study is in concordance with our hypothesis. The finding for astrocytomas offers indirect radiological evidence that the defect in BBB which causes edema is etiologically related to the defect in the BBB responsible for contrast enhancement. We have also found significant association between the degree of contrast enhancement and the volume of peritumoural edema found in MRI with histopathological subtypes of diffusely infiltrating intracranial astrocytomas. The findings suggest that astrocytoma subtypes have a characteristic profile of MRI.

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The Sitting Position in Neurosurgery: A Clinical Study in 30 Cases

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Abstract:

Objective: *Sitting position for operation of posterior fossa lesions, occipital and posterior parietal lesions, foramen magnum, upper cervical spinal lesions provides an excellent visualization because of slack of brain due to gravity drainage of CSF and blood. Hence gross total tumour removal relatively easy and less complicative.* ***Methods:*** *From January 2008 to march 2010 total 30 cases underwent neurosurgical procedure in sitting position. Physical characteristics including patients age, sex, size of the tumour and histological diagnosis were collected. The post operative image were studied to see the extent of tumour removal and early detection of complications. Almost all patients required peroperative cerebral venous line or peripheral inserted central venous line, precordial doppler sound, $ETCO_2$, O_2 saturation and close monitoring of blood pressure.* ***Results:*** *Venous air embolism were detected in two cases (6.6%). Total tumour removal was possible in 17 (56.6%) cases and subtotal in 11 (36.6%) cases. There were 4 (13.33%) mortality in thirty cases, two cases from CP angle tumour and another case from petroclival meningioma and another from pineal region tumour. There was pneumocephalus in almost all cases and post-operative new facial paresis in 10 (33.3%) cases. Fifth cranial nerve palsy developed in 3 (10%) cases. Temporary lower cranial nerve palsy developed in 2 cases. Post-operative tumour bed haematoma developed in 4 (13.33%) cases. Most of the patient had good outcome (GOS 5).* ***Conclusion:*** *Sitting position can be safely done with good preoperative physiological, peroperative close monitoring of the patient regarding blood pressure, $ETCO_2$ and oxygen saturation. However postoperative complication like tumour bed haematoma, pneumocephalus, cranial nerve palsy have to be bring in mind.*

Introduction:

The use of the sitting or semisitting position for patients undergoing posterior fossa and/or cervical spine surgery facilitates easy surgical access but presents a physiological challenges for the anaesthetist[1]. This patient position provides optimum access to midline, paramedian and cerebellopontine lesions it also improves cerebral venous drainage, lowers intracranial pressure (ICP) and promotes gravity drainage of blood and cerebral spinal fluid (CSF)[2,3].Complications related to the use of this position includes haemodynamic instability, venous air embolism (VAE), embolism related hypoxia and/or hypotension, with the possibility of paradoxical air embolism, pneumocephalus, quadriplegia and compressive peripheral neuropathy[1-3]. Alternative positions for surgical access to the posterior fossa and the cervical spine include the prone, park bench, lateral positions. Prolonged neurosurgical procedures with pin fixation of the head in semisitting positions necessitate extensive patient monitoring to ensure cardiorespiratory homeostasis[1-3].

The objective of this study is to provide a risk-benefit analysis of the present day use of the sitting position for patients undergoing CP angle, midline posterior fossa and cervical spine surgery.

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Since 1913 when the first surgery with the patient in sitting position was performed, the debate concerning this positioning has continued. The sitting position is thought to be best for surgical access to CP angle, midline and paramedian posterior fossa or to posteriorly located parietal lesions[4]. Gravity facilitates drainage of blood and other fluids and an optimal view over the pathology is possible with lowered intracranial pressure and increased venous return[1-4].

Air embolism can occur during any surgical procedure in which the operative site is 5 cm or higher above the right atrium[4].

The higher chance of venous air embolism occur in the presence of persistent foramen ovale (PFO)[5]. In patient with PFO surgical opening of veins can lead to a paradoxical air embolism with critical cerebral and cardio-pulmonary complication. PFO have found in 28% of adult patients using transesophageal echocardiography as diagnostic procedure[5]. Doppler ultrasound is the most sensitive noninvasive monitor, and is commonly used in sitting position. The monitor uses ultrahigh frequency sound waves (usually between 2 and 3 megahertz) to measure blood flow velocity and changes in blood density. This information is converted to a characteristic sound[5,6].

Transesophageal echocardiography is more sensitive than Doppler ultrasound, and is also more invasive and technically more difficult to place and to interpret. It does, however, allow determination of the volume of air aspirated. Transesophageal echocardiography will also show air passing through a patent foramen ovale into the left atrium and into the systemic circulation[5-7].

Monitoring of End-tidal carbon dioxide is commonly used, widely available, and sensitive. It is highly sensitive but not specific for air embolism. It becomes low at the beginning of venous air embolism. However hyperventilation, low cardiac output, other types of emboli, and COPD can also decrease ETCO2[7,8].

The least sensitive monitor is the precordial or esophageal stethoscope. A “millwheel murmur” indicates a massive air embolism. When a millwheel murmur is heard, cardiovascular collapse is imminent[7,8].

A multiorifice central venous catheter should be placed in patients at risk of air embolism. The optimal site for the tip of the catheter is at the SVC-RA junction. If an embolus occurs, air can be aspirated through the catheter before it enters the pulmonary circulation[5-8].

Treatment of air embolism is largely supportive. The surgeon should be informed as soon as the diagnosis is made. N2O diffuses into air bubbles faster than nitrogen can diffuse out, and increases the size of the bubble. If N2O is used, it should be discontinued when an air embolism occurs. FiO2 (fraction of inspired O_2) should be increased to 1.0. The surgeon should flood the surgical field with fluids while open veins are cauterized or exposed bony emissary vein is waxed. If significant amounts of air have entered the circulation, the jugular veins should be manually occluded. This will prevent additional air from being entrained while the surgeons obtain hemostasis. The blood pressure should be supported with fluid and vasopressors[8].

Controversy surrounds the use of the sitting position for neurosurgery, regarding the risk of venous air embolus (VAE) and its sequelae. The reported incidence of VAE in adults undergoing neurosurgery in the sitting position varies from 7 to 50%[8].

Methods:

From January 2008 to march 2010 total 30 cases underwent neurosurgical procedure in sitting position. Physical characteristics including patient’s age, weight, and histological diagnosis were collected. The post-operative notes were studied together with the follow up notes to document any unexpected neurological sequelae. Almost all patients required CV line or peripheral inserted central venous catheter, precordial doppler sound, $ETCO_2$, O_2 saturation and close monitoring of blood pressure. Routine use of normal saline irrigation to the operation field, regular use of bone wax to the bone emissary vein, bilateral jugular vein compression before starting of dural incision to locate the transverse and sigmoid sinus and minimum cautery to the tumour bed. To achieve

hemostasis we raise the blood pressure 20mm of Hg above the preinduction blood pressure and again bilateral jugular vein compression to exclude any venous bleeding before closure of dura.

Internal acoustic meatus was Drilling of most of the cases of acoustic schwannomas. We didnot use facial nerve monitor to trace out the location of facial nerve because of its nonavailability in our institute. We did routine practice of raising the blood pressure before closing the dura and bilateral jugular vein compression to check the operative site bleeding. Drilled Internal acoustic meatus was filled by subcutaneous fat. Fibrin glue were used in some cases to make the the dural closure water tight. In some cases we used acrylic bone cement to close the lateral suboccipital craniectomy defect followed by suboccipital muscle and subcutaneous tissue and skin closure.

Results:

Demographic study from table I revealed age group between 25 and 65 (median 40, average 45), among them 16 (53.3%) were male and 14 (46.7%) were female patients (Table-II).

Table-I

Shows distribution of age group:

Age	No. of Patient
21-30	3 (10%)
31-40	10 (33.3%)
41-50	9 (30%)
51-60	7 (23.3%)
61-70	1(3.3%)

Table-II

Shows distribution of sex group:

Sex	No. of Patient
Male	16 (53.3%)
Female	14 (46.6%)

Headache and vomiting was presented in most of the cases (27 patients), deafness in 18 cases, facial weakness were in 3 patients, ataxia in 24 cases, quardriparesis were seen in 3 cases (Table-III).

Table-III

Shows distribution of presentation group:

Presentation	No. of Patients
Headache	27 (90%)
Vomiting	27 (90%)
Deafness	18 (60%)
Facial Weakness	5 (16.6%)
Ataxia	24 (80%)
Quadriparesis	3 (10%)

CP angle tumour were 60%, petroclival meningioma were 20%, foramen lesions were 6.6%, pineal region tumour were 10%, upper cervical schawnnoma 3.3% . Total tumour removal was possible in 11 (36.6%) cases and subtotal in 17 (56.6%) cases (table-IV).

Table-IV

Location of Lesions:

Location	No of Patients
Cerebellopontine angle	18 (60%)
Petroclival Meningioma	6 (20%)
Foramen Magnum Schwannoma	1(3.3%)
Foramen Magnum Meningioma	1(3.3%)
Pineal Region Tumour	3 (10%)
Upper cervical Schawnnoma	1(3.3%)
Total	30

Gross total tumour removal was possible in 11 (36.6%) cases(Figure 1,2,4,5) and subtotal removal in 17 (56.6%) cases (figure 5, 6, 7, 8) and partial removal in 2 (6.66%) cases.

Facial nerve preservation could possible in 10 cases (55%) (Figure 5, 8) and not possible in 8 cases (45%) out of cases of 18 CP angle tumour.

There were 4 (13.33%) mortality in thirty cases, two cases from CP angle tumour one case from petroclival meningioma and another from pineal region tumour. There were pneumocephalus in almost all cases and post-operative new facial paresis in 13 (13.3%) cases. 5^{th} nerve palsy developed in 3 (10%) cases, lower cranial nerve palsy developed in 2 cases (6.6%). Post-operative tumour bed haematoma developed in 4 (13.33%) cases. Among them 2 cases underwent urgent re-exploration and hematoma evacuation. Most of the patients have good outcome (GOS 5) (Table-V).

Table-V

Complications of sitting position:

Complications	No. of Patients
Facial nerve palsy	10 (33.3%)
5th nerve palsy	3 (10%)
Lower cranial nerve palsy	2 (6.6%)
Hematoma	5 (16.6%)
Hydrocephalus	3 (10%)
Cerebellar swelling	3 (10%)
Venous air embolism	2 (6.6%)
Pseudomeningocele	3 (10%)
Cervical cord injury	Nil

Discussion:

For many neurosurgeons the sitting position (Figure 1 & 2) offers the advantages of optimal surgical exposure, better anatomic orientation, improved cerebral venous drainage, lower intracranial pressure, and enhanced gravity drainage of blood and cerebrospinal fluid[7]. Because life threatening complications can occur during neurosurgery in the sitting position hence caution is advocated in almost all patients including patients with a patent foramen ovale, atherosclerotic cardiovascular disease, severe hypertension or cervical stenosis[7,8].

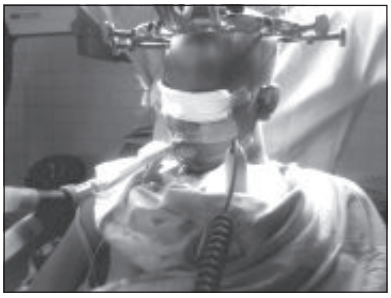

Fig.-1: *Front view of sitting position with head fixation by 4 pin head fixator and precordial Doppler.*

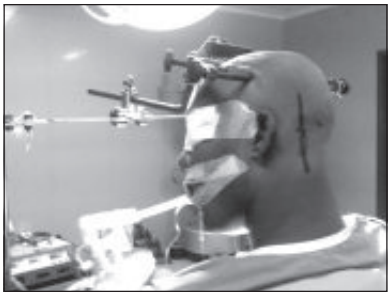

Fig.-2: *Back view of sitting position.*

Cervical cord injury is one of the most serious complications after surgery in sitting position. In 1980, Hitselberger and House reported five cases of midcervical quadriplegia after acoustic tumour resection performed with the patient in the sitting position. They suggested that acute diffuse infraction was caused by direct prolonged[9]. Pressure on cervical cord related to a preexisting spondylotic bar at the midcervical level[9].

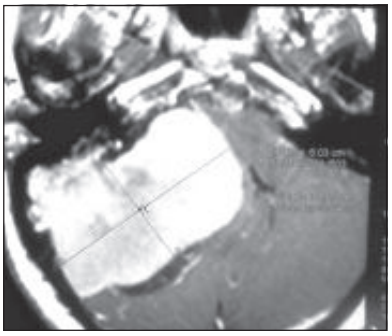

Fig.-3: *Shows pre-op posterior petrosal meningioma.*

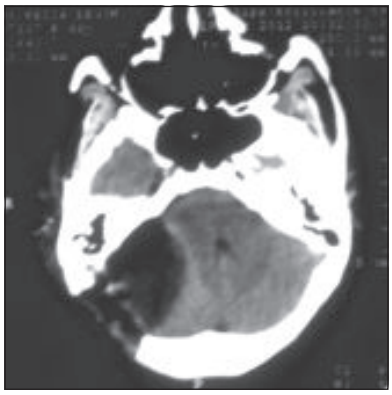

Fig.-4: *Shows post-op picture of posterior petrosal meningioma.*

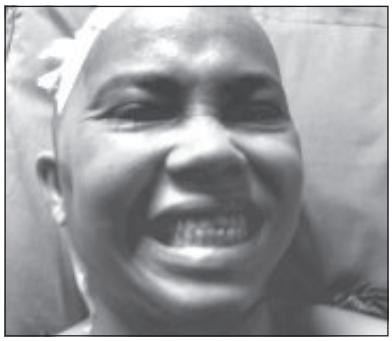

Fig.-5: *Shows post-op picture of face showing no weakness.*

The highest concern is the risk of VAE and its sequelae. Although there are several published reports of the incidence of VAE in the sitting of adults, there are no large series that look at the incidence of VAE in children. The reported incidence as detected by transoesophageal doppler ultrasonography in adults ranges from 7 to 50%. In another study its incidence is 35%[9,10].

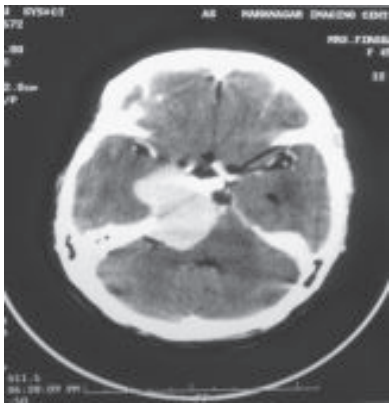

Fig.-6: *Shows preoperative picture of petroclival meningioma.*

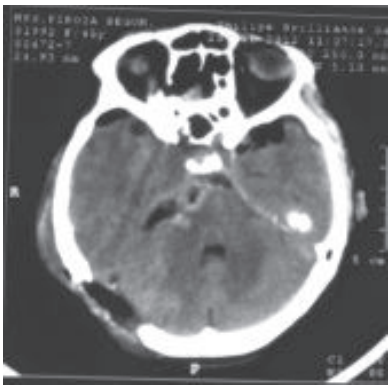

Fig.-7: *Shows post operative picture of petroclival meningioma showing small residual tumour.*

Fig.-8: *Shows postoperative picture of having no facial weakness.*

In our study venous air embolism occurred in 2 patients (6.6%), which is still lower than other the previous reports. We believe that the care taken while positioning the patient and the meticulous prevention of bleeding from surgically opened venous vessels & bony emissary vein were responsible for the lower air embolism rate[10]. For quick detection and management we have routinely used precordial Doppler(Figure -9) and cavafix(peripheral inserted central venous line (Figure-10).

Fig.-9: *Shows pheripheral inserted central venous catheter.*

Fig.-10: *Shows fetal doppler used as precordial doppler over the chest.*

The effect of an air embolus depends both upon the rate and volume of air introduced into the circulation. The capacity of the lung to filter microbubbles of air from the venous circulation is exceeded when gas enters the circulatory system at a rate greater than 0.30 ml/kg per minute in a canine model; infusions at greater rates generally result in arterial emboli and tissue ischemia[11].

Large, rapid boluses of air are tolerated less well than slow infusions of small amounts of air. It is estimated that 300 to 500 ml of gas introduced at a rate of 100 ml/sec is a fatal dose for humans[11].

When air enters the veins, it travels to the right side of the heart, and then to the lungs. This can cause the vessels of the lung to constrict, raising the pressure in the right side of the heart. If the pressure rises high enough in a patient who is one of the 20-30% of the population with a patent foramen ovale, the gas bubble can then travel to the left side of the heart, and on to the brain or coronary arteries. Such bubbles are responsible for the most serious of gas embolic symptoms[12].

Some studied have stated relative and absolute contraindications for the sitting position. Alongside age, hypertension and obstructive lung disease, diagnosed PFO is one of them. In a study by Kwapisz and colleagues the semi-sitting position chosen before operation was changed into supine position after diagnosing PFO to avoid complications[12].

Contraindications to use the operative sitting position:

Absolute:

Patent ventriculo-atrial shunt.

Right atrial pressure in excess of left atrial pressure Patent foramen ovale.

Cerebral ischemia when upright and awake.

Relative:

Extremes of age.

Uncontrolled hypertension.

Chronic obstructive airway disease.

Certain pre-existing conditions may place patients at increased risk of venous air embolism (i.e. presence of a patent ventriculo-atrial shunt, demonstrable pressure gradient from left to right heart or presence of a patent foramen ovale). Patients who experienced cerebral ischemia in upright position as a result of cardiovascular and cerebrovascular disease are at increased risk of inadequate cerebral perfusion under anesthesia in the operative sitting position. Relative contraindications may include extremes of age, uncontrolled hypertension or chronic obstructive air way disease[12].

Conclusion:

Sitting position can be safely done with good preoperative physiological, peroperative close monitoring of the patient regarding blood pressure, $ETCO_2$ and oxygen saturation. However, postoperative complications like tumour bed haematoma, pneumocephalus, and cranial nerve palsy have to be bring in mind. Preoperative echocardiography investigation for detection of PFO further reduces the risk to the patient in that knowledge of the presence of PFO will heighten the surgeons degree of care and focus attention on alternative neurosurgical positions for surgery.

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REVIEW ARTICLE

Alzheimer's Disease - An Update

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Introduction:

Alzheimer's (AD) disease is a progressive and fatal neurodegenerative disorder manifested by cognitive and memory deterioration, progressive impairment of activities of daily living and a variety of neuropsychiatric symptoms and behavioral disturbances[1].

This incurable, degenerative, and terminal disease was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him[2]. Alzheimer's disease is the most common cause of dementia occurring mostly in patients over 45 years[3]. Generally, it is diagnosed in people over 65 years of age[4], although the less-prevalent early-onset Alzheimer's can occur much earlier. It is one of the most frequent mental illnesses, making up some 20 percent of all patients in psychiatric hospitals and a far larger proportion in nursing homes [4].

The incidence rate of clinically diagnosed Alzheimer disease is similar throughout the world, and it increases with age, approximating 3 new cases yearly per 100,000 persons younger than age 60 years and a staggering 125 new cases per 100,000 of those older than age 60 years. In India incidence rate is 324/100000/year above 65 yrs and 174/ 100000/year above 55 yrs .There is no exact epidemiological data of AD in Bangladesh.

The prevalence of the disease per 100,000 populations is near 300 in the group aged 60 to 69 years; it is 3,200 in the 70- to 79-year-old group and 10,800 in those older than age 80. In the year 2008, there were estimated to be more than 2 million persons with Alzheimer disease in the United States. Prevalence rates, which depend also on overall mortality, are 3 times higher in women, although it does appear that the incidence of new cases is only slightly disproportionate in women[5].

Life expectancy of the population with the disease is reduced[6]. The mean life expectancy following diagnosis is approximately seven years.[7] Fewer than 3% of patients live more than fourteen years[8].

Without advances in therapy, the number of symptomatic cases in the United States is predicted to rise to 13.2 million by 2050[1]. Alzheimer's disease is predicted to affect 1 in 85 people globally by 2050[5]. The association between the pathological features of Alzheimer's disease and dementia is stronger in younger than in older[9]. About 15% of cases are familial and this cases fall into two main groups, an early onset dominant pattern and a later onset group whose inheritance is not so clear[10]. Approximately 10% of all person over the age of 70 years have significant memory loss and in more than half the case is AD[11].

Pathology:

Pathology of AD includes neurofibrillary tangles, senile plaques at the microscopic level. Neurofibrillary tangles and senile plaques were described by Alois Alzheimer's in his original report on the disorder in 1907. They are now universally accepted as a hallmark of the disease. These lesions accumulate in small numbers during normal aging of the brain but occur in excess in AD[12].

Neuropathlogical lesions of Alzheimer's disease like amyloid and diffuse neuritic plaques & neurofibrillary tangles in the entorhinal,

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hippocampal, frontal, temporal, parietal and occipital cortexes.(Figure1). Cortical atrophy was assessed macroscopically in each brain area without knowledge of microscopical findings[10].

Pathogenesis & Pathophysiology:

There is increasing evidence to suggest that soluble amyloid fibrils called oligomers lead to the dysfunction of the cell and may be the first biochemical injury in Alzheimer's disease. Misfolded Aβ42 molecules may be the most toxic form of the protein. Accumulation of oligomers eventually leads to formation of neuritic plaques. The neuritic plaques contain a central core that includes Aβ amyloid, proteoglycans, Apo E4, α1 antichymotrypsin and other proteins. Aβ amyloid is a protein of 39-42 amino acids that is derived proteolytical from a larger transmembrane protein named amyloid precursor protein when amyloid precursor protein is cleaved by β & γ secretases. The plaque core is surrounded by the debris of degenerating neurons, microglia and macrophages. The accumulation of Aβ amyloid in cerebral arterioles is termed amyloid angiopathy[12] (Figure 2) . Vascular endothelial cells have a central role in the progressive destruction of cortical neurons in Alzheimer's disease. In Alzheimer's disease the brain endothelium secretes the precursor substrate for the b-amyloid plaque and a neurotoxin peptide that selectively kills cortical neurons. Large population of endothelial cells are activated by angiogenesis due to brain hypoxia and inflammation[13] . Cell loss occurs particularly from the deeper layers of the cortex and preferentially involves large neurons. Synapse loss or neuron loss provides the highest correlation with global cognitive impairment[11].

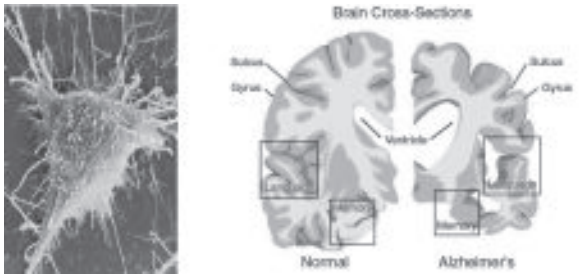
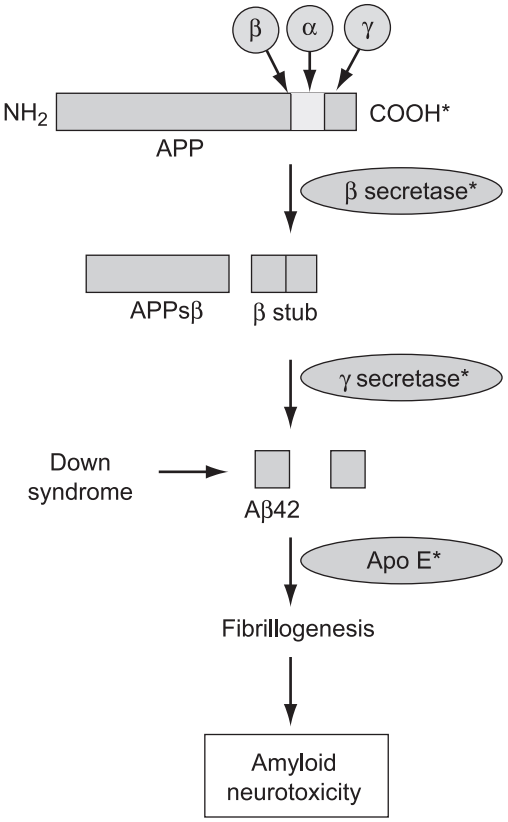


Fig.-1: *Pathological changes in Alzheimer's disease (AD).*



Source: Ropper AH, Samuels MA: Adams & Victor's Principles of Neurology 9th Edition: http://www.accessmedicine.com

Fig.-2: *Pathogenesis: amyloid neurotoxicity*

Neurofibrillary tangles are silver-staining, twisted neurofilaments in neuronal cytoplasm that represent abnormally phosphorylated tau protein. Tau is a microtubule associated protein that may function to assemble and stabilize the microtubules that convey cell organelles, glycoproteins and other important materials throughout the neuron. The ability of tau protein to bind to microtubule segments is determined partly by the number of phosphate groups attached to it. Increased phosphorylation of tau protein distorts this normal process[12].

In 2009, this theory was updated, suggesting that a close relative of the beta-amyloid protein, and not necessarily the beta-amyloid itself, may be a major culprit in the disease. The theory holds that an amyloid-related mechanism that prunes neuronal

connections in the brain in the fast-growth phase of early life may be triggered by aging-related processes in later life to cause the neuronal withering of Alzheimer's disease[14]. N-APP, a fragment of APP from the peptide's N-terminus, is adjacent to beta-amyloid and is cleaved from APP by one of the same enzymes. N-APP triggers the self-destruct pathway by binding to a neuronal receptor called death receptor 6 (DR6, also known as TNFRSF21)[15]. DR6 is highly expressed in the human brain regions most affected by Alzheimer's, so it is possible that the N-P/DR6 pathway might be hijacked in the aging brain to cause damage. In this model, Beta-amyloid plays a complementary role, by depressing synaptic function.

Biochemically, AD is associated with a decrease in the cerebral cortical levels of several proteins and neurotransmitters especially acetylcholine, its synthetic enzyme choline acetyltransferase and nicotinic cholinergic receptors. There is also reduction in norepinephrine levels in brain stem nucleus[12].

There are no biologic markers for Alzheimer's disease or most other dementias but with careful evaluation and the application of well defined, reliable clinical criteria, diagnosis can be made with component of the workup in careful

Diagnosis:

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, now known as the Alzheimer's Association) established the most commonly used NINCDS-ADRDA Alzheimer's Criteria for diagnosis in 1984[17], extensively updated in 2007[18]. These criteria require that the presence of cognitive impairment, and a suspected dementia syndrome, be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD.

Table-I

*Criteria For The Diagnosis Of Alzheimer's disease**

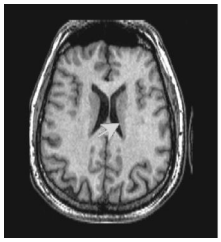
Diagnosis	Criteria	
Probable	Alzheimer's disease	All of the following must be present: Dementia established by examination and documented by objective testing Impairment in memory and at least one other cognitive function (e.g., language or perception). Progressive worsening of memory and at least one other cognitive function. No disturbance in consciousness
		Onset between 40 and 90 years of age. Absence of another brain disorder or systemic disease that might cause dementia. In addition, the diagnosis may be supported by one or more of the following: Loss of motor skills.
		Diminished independence in activities of daily living and altered patterns of behavior. Family history of similar disorder. Laboratory results consistent with the diagnosis (e.g., cerebral atrophy on computed tomography).
Possible	Alzheimer's disease	Fulfillment of the above criteria with variation in the onset of symptoms or manifestations or in clinical course; or a single, but gradually progressive, cognitive impairment without an identifiable cause.
		Another brain disorder or systemic disease that is sufficient to produce dementia, but that is not considered to be the underlying cause of the dementia in the patient.
Definite	Alzheimer's disease	Fulfillment of the above clinical criteria and histologic evidence of Alzheimer's disease based on examination of brain tissue obtained at biopsy or autopsy.

*Criteria were adapted from Mc Khann et al.

Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia[19].

A new technique known as PiB PET has been developed for directly and clearly imaging beta-amyloid deposits in vivo using a tracer that binds selectively to the A-beta deposits [20]. Recent studies suggest that PiB-PET is 86% accurate in predicting which people with mild cognitive impairment will develop Alzheimer's disease within two years, and 92% accurate in ruling out the likelihood of developing Alzheimer's disease[21].

Assessment of intellectual functioning including memory testing can further characterise the state of the disease[22]. Screening for depression, vitamin B 12 deficiency, and hypothyroidism should be performed. Screening for syphilis is not justified unless there is a clinical suspicion of neurosyphilis. The diagnosis can be confirmed with very high accuracy, post-mortem when brain material is available and can be examined histologically[23].



Normal aging
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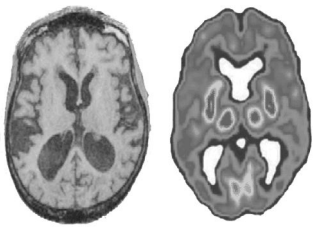

Scans of Patients with Probable Alzheimer's Disease. In Panel A, a magnetic resonance image shows cortical atrophy and ventricular enlargement. In Panel B, a positron-emission tomographic scan shows reduced glucose metabolism in the parietal lobes bilaterally (blue-green) as compared with more normal metabolism in other cortical areas (yellow).

Management:

Guidelines for Management of Dementia are described as follows.

Standards:

Use of cholinesterase inhibitors should be considered in patients with mild-to-moderate Alzheimer's disease, although the benefit is limited.

Antipsychotic agents should be used to treat agitation and psychosis when environmental manipulations fail.

Behavior modification and scheduled toileting are helpful to reduce urinary incontinence.

Guidelines:

Use of vitamin E should be considered in an attempt to slow the progression of Alzheimer's disease.

Use of antidepressant medications should be considered for patients with depression.

Educational programs can be supportive for caregivers and nursing-home staff.

* The guidelines are based on those of the Quality Standards Subcommittee of the American Academy of Neurology.

Cholinesterase inhibitors are approved for the treatment of mild-to-moderate Alzheimer's disease and should be considered as a standard of care for patients with Alzheimer's disease. Four cholinesterase inhibitors are available: tacrine, donepezil, rivastigmine, and galantamine (Table-II)[24].

Side effects reported in clinical trials of cholinesterase inhibitors included nausea, vomiting, and diarrhea, as well as weight loss, insomnia, abnormal dreams, muscle cramps, bradycardia, syncope, and fatigue[25].

Memantine (Table-II), an *N*-methyld-aspartate antagonist recently approved by the Food and Drug Administration (FDA) for the treatment of moderate-to severe Alzheimer's disease may interfere with glutamatergic excitotoxicity or may provide symptomatic improvement through effects on the function of hippocampal neurons[26]. A double-blind, placebo- controlled trial of memantine in patients with moderate-to-severe Alzheimer's disease showed the superiority of memantine over placebo as indicated by both the Activities of Daily Living Inventory and the Severe Impairment Battery (a neuropsychological test for patients with severe dementia),but not on the Global Deterioration Scale[27].

Major depression occurs in 5 to 8 percent of patients with Alzheimer's disease[28]. Up to 25

Table-II

*Clinical Pharmacology of Agents Useful for Reducing the Signs of Dementia.**

Characteristic	Donepezil	Rivastigmine	Galantarmine	Memantine
Time to maximal serum concentration (hr)	3-5	0.5-2	0.5-1	3-7
Absorption affected by food	No	Yes	Yes	No
Serum half-life (hr)	70-80	2h	5-7	60-30
Protein binding (%)	%	40	0-20	45
Metabolism	CYP2D6, CYP3A4	Nonhepatic	CYP2D6, CYP3A4	Nonhepatic
Dose (initial/maximal)	5 mg daily/ 10 mg daily	1.5 mg twice daily/ 6 mg twice daily	4 mg twice daily/ 12 mg twice daily	5 mg daily/ 10 mg twice daily
Mechanism of action	Cholinesterase inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor	NMDA-receptor antagonist

CYP2D6 denotes cytochrome P-450 enzyme 2136, CYP3A4 cytochrome P-450 enzyme 3A4, and IN MDA N-methyl-D-aspartate.
y Rivastigmine is a pseudo-irreversible acetylcholinesterase inhibitor that has a eight-hour half-life for the inhibition of acetylcholinesterase in the brain.

percent have depressed mood at the time of onset of memory loss. Few studies of the use of antidepressant drugs in patients with Alzheimer's disease have been published, although these drugs are frequently used [29].

The effects of the tricyclic antidepressant imipramine were similar to those of placebo in alleviating depression in 61 patients with Alzheimer's disease [30]. In a crossover study of 26 depressed patients with Alzheimer's disease, in which clomipramine and placebo were each given for six weeks, both treatments resulted in a 40 to 50 percent reduction in the score on the Hamilton Depression Rating Scale [31].

Delusions and psychotic behavior increase with the progression of Alzheimer's disease and, once present, are persistent in 20 percent of patients. Agitation may coexist in up to 20 percent more patients, and it tends to increase with advancing disease [32]. In a study comparing high-dose haloperidol (2 to 3 mg per day), low-dose haloperidol (0.5 to 0.75 mg per day), and placebo in 71 patients with Alzheimer's disease and psychosis or disruptive behavior, the high dose produced a 30 percent greater improvement than either placebo or the low dose.

Alpha-tocopherol and selegiline delay the development of the later stages of Alzheimer's disease, but it is difficult to say whether a delay of 20 to 30 weeks is meaningful in a disease that lasts a decade or more [33].Unlike selegiline, alpha-tocopherol does not interact with other drugs and therefore can be administered to the majority of patients, regardless of other treatments for Alzheimer's disease. The studies of idebenone, propentofylline, and *Ginkgo biloba* provide no clinically meaningful information on the basis of which to make treatment recommendations [34].

As of August 2010 there were more than 812 clinical trials under way to understand and treat Alzheimer's disease. There were 149 of these studies in the last phase before commercialization (phase three trials) [35].

Amyloid beta is a common target, existing many trials which aim to reduce it with different agents such as bapineuzumab, an antibody in phase III for patients in the mild to moderate stage, semagacestat, a ã-secretase inhibitor, MPC-7869, and acc-001, a vaccine to amyloid beta in phase II to be used in the mild stage. However, in a recent study an experimental vaccine was found to have cleared patients of amyloid plaques but did not have any significant effect on their dementia, casting doubt on the utility of such approaches[36]. Other approaches are neuroprotective agents, like AL-

108 (phase II completed); or metal-protein interaction attenuation, as is the case of PBT2 (phase II completed) [37]. Finally, there are also many basic investigations trying to increase the knowledge on the origin and mechanisms of the disease that in the future may help to find new treatments.

Conclusion:

Current treatments for patients with Alzheimer's disease target the biochemical pathway that is associated with the disease and is considered amenable to modification.. Therapeutic approaches should focus on methods to prevent or delay the progression of Alzheimer's disease.The development of such approaches will depend on increasing our knowledge of the pathophysiology of the disease.

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CASE REPORTS

Protein S Deficiency: Ischemic Stroke in Young adult – A Case Report

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Abstract:

Stroke is the third most common cause of mortality in Westernised countries and

Accounts for 12% of all deaths in the UK. The economic cost of stroke is enormous. Twelve per cent of first strokes occur in patients under 45 years of age, of which approximately 50% are ischaemic in nature. Stroke in young adult poses a major health problem. The causes of ischaemic stroke in young adults are many and diverse.Such patients usually require more extensive investigations in order to find an underlying cause than more elderly patients. Principal causes are cardioembolism, premature atherosclerosis, haematological and immunological disorders and migraine. Thrombophilic factors have been implicated in 4-8% of the young adult strokes worldwide. Protein S deficiency is a rare cause of ischemic stroke in young population. Only a few sporadic cases have been described in the literature. We are reporting a case of protein S deficiency-related ischemic stroke in a 40-year-old man. Early diagnosis and targeted approach can help such patients to prevent recurrent thrombotic episodes.

Keywords: *Protein S deficiency, Ischemic stroke, young adult stroke*

Introduction:

Protein S is a vitamin K-dependent plasma protein that potentiates the inactivation of factors Va and VIIIa by protein C[1]. Hereditary deficiency of free protein S (FPS), the active form, results in a prothrombotic state and has been associated with both recurrent venous thrombosis[2-4] and arterial thrombosis.[5,6] The overall estimated incidence of deep vein thrombosisis is one episode for every 1,000 persons. Protein S deficiency has been also found to be associated with cerebrovascular occlusion, although the exact role is controversial. More recently, FPS deficiency has gained recognition as a possible risk factor for ischemic stroke. Case reports[7-10] have suggested that familial FPS deficiency may play a causative role in young patients with cryptogenic stroke. Acquired FPS deficiency has been reported as a possible cause of cerebral infarction in patients with nephrotic syndrome[11] and inflammatorybowel disease.

Case Report

A 40-year-old smoker, normotensive, nondiabetic, right handed person, presented to our hospital 1 month back with history of sudden onset weakness of right half of the body & deviation of angle of mouth towards left side for last 12 hrs .He also had speech difficulties in the form of difficulty in naming objects with emotional lablity at that time. His condition was initially detetriorating for first few hours then became static. He had no history of trauma, headache, vomiting blurring of vision, or any history of fever prior to onset of this illness. No similar episode occurred before. Family history was negative for vascular events or other predisposing factors for stroke.

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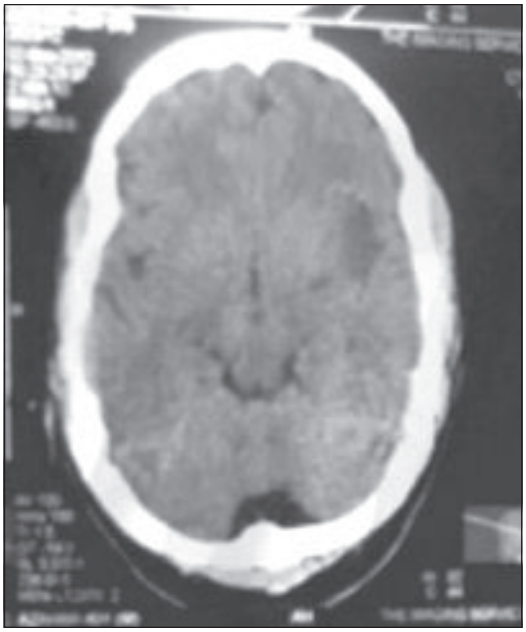

Fig.1: *Illdefined hypodense areas are seen in left fronto-parietal regions suggestive of acute cerebr.*

Discussion

Stroke in young adult population has a high incidence of approximately 24–35%, according to some studies in India. Abraham *et al*[12]. from Vellore reported an incidence of 25% in population less than 40 years of age. Munts *et al*[13] reported that idiopathic coagulation disorders were found in about a quarter of young stroke patients, although the clear-cut data has been lacking from India. Carod-A *et al*[14] studied about ischemic stroke subtypes and prevalence of thrombophilia in Brazilian stroke patients. They examined 130 consecutive young and 200 elderly patients. Prevalence of thrombophilia was, respectively: protein S deficiency (11.5% versus 5.5%), protein C deficiency (0.76% versus 1%). They concluded that prothrombotic conditions were more frequent in stroke of undetermined causes.

The importance of thrombophilic disorders in arterial stroke has been debatable. Ischemic stroke has been reported as a rare manifestation of protein S deficiency. Girolami *et al*.[15] and Sie *et al*.[16] were among the first who reported the association of familial deficiency of protein S as a cause of ischemic stroke in young. Wiesel *et al*.[17] studied 105 patients with protein S deficiency, out of which 14 had arterial thrombotic accidents involving the central nervous system or the myocardium, while most studies revealed a weaker association between the two.[18] Douay *et al*.[19] reported that hereditary deficiencies of coagulation inhibitors are rare in ischemic stroke patients under 45 years and their systematic detection seems to be of poor interest. Mayer *et al*.[20] also supported the fact that acquired deficiency of free protein S is not a major risk factor for ischemic stroke.

In this 40-year-old patient without any risk factors, the acquired factor S deficiency possibly played a role in the ischemic stroke. Factor S deficiency should be considered in venous stroke, recurrent pulmonary embolism, unusual site of venous occlusion, family history of vascular events, and stroke in young population. Aetiology of such vascular events in young must be thoroughly investigated so as to guide prevention and treatment of this devastating disease. Measurement of total and free protein S levels should be a part of the evaluation for any young adult who has had a stroke.

Clinical examination revealed a young confused man. Pulse rate was 84/min,Blood pressure 130/80 mm Hg and respiratory rate was18/min.His GCS was 13, with nominal aphasia. Cranial nerve examination revealed right sided upper motor type facial nerve palsy.Motor findings consistent with right-sided hemiplegia having muscle power 0/5 on the right side, but 5/5 on the left side,deep tendon reflexes were brisk in the right side but normal in the left side, plantars were extensor in the right side with flexor in the left side.Cerebellar & sensory function could not be performed.

CT head [Figure 1] revealed ill-defined hypodense areas are seen in left fronto-parietal regions suggestive of acute cerebral infarct (left).Routine hematological investigations, haemoglobin level was 16.2 g/dl,total leucocyte count was 13000/cumm with normal differentials.Platelet count was 200 000/cumm. Serum electrolytes & serum creatinine report was normal.ECG & Chest x-ray did not reveal any abnormality. The patient was negative for HIV, syphilis and hepatitis B serology. Other factors were tested included FBS, lipid profile, coagulation

profile, echocardiography including both transthoracic & transesophageal, and duplex scanning of neck vessels were unremarkable. Vasculitis profile was negative.

Workup for thrombophilias revealed reduced protein S function (18% of normal) alongwith protein C; , antithrombin III, anticardiolipin antibodies, and lupus anticoagulant, homocysteine were within normal limits. A diagnosis of protein S deficiency was kept and the patient was managed with low molecular weight heparin followed by oral anticoagulants. Neurological functions improved, muscle power became 4/5,completely recovered from nominal aphasia and patient was discharged two weeks after initiation of treatment.He was advised to take oral anticoagulants & for regular follow up at stroke clinic with INR after 1 week & planned for repeat protein S after after 3 months.

Conclusion:

Stroke is one of the foremost causes of morbidity,mortality & a socioeconomic challenge, more so in Bangladesh where health system including the rehabilitation is not the reach of oridinary people. It is crystal clear that, this devastating condition affecting the young adult group, not only affects the patient but also their family , as well as the economy of whole nation. Protein S deficiency is rare cause of ischemic stroke. Patient with protein S dficiency has got tendency to reccurent thrombotic events. So, early diagnosis & targeted approach can save life & prevent further events.

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Embolic Stroke and Pulseless Right Arm in a Schoolgirl with Arterial Thoracic Outlet Syndrome: A Case Report

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Abstract:

A rare clinical presentation arterial Thoracic outlet syndrome (TOS) is described in a young school-girl. TOS causing distal; disease is a rare cause of artery to- artery embolic stroke. Brain-stem ischemic stroke is a result of compromise to the posterior circulation. This is often due to antegrade embolism from the heart or proximal vessels. Retrograde blood flow has been described in the subclavian artery, thus making the distal subclavian artery a source of possible retrograde embolism to carotid circulation[1]. Clinical presentation also included left hemiparesis caused by right subclavian artery thrombosis and retrograde embolizatoin of thrombus via common carotid artery to the right middle cerebral artery (MCA) distribution[2].

Keywords: *Thoracic outlet syndrome; arterial Thoracic outlet syndrome; subclavian artery*

Case Report:

A15 years old girl normotensive nondiabetic right handed school-girl admitted with the history of episodic unilateral headache followed by sudden onset of left side weakness with focal convulsion. She had a episodic headache 6 months back. Each episode started with blurring of vision followed by unilateral throbbing headache associated with vomiting persisted for several hours & relieved spontaneously. Headache was aggravated by light and sound and patient felt comfortable in dark place. One month back patient developed sudden severe global headache without vomiting and suddenly fell in the ground followed by left sided weakness and repeated convulsion on the left side of body. She had no history of eye or neck pain nor any history of fever or joints pain, morning stiffness, rash, oral ulcer, hair loss, photosensitivity, abdominal pain, leg ulcer, bone pain, chest pain, palpitation, exertional dyspnoea, migratory arthritis, or any bleeding manifestations. She did not give any history of right arm pain suggestive of claudication or transient loss of consciousness and did not have any permanent neurologic deficit previously and she had not sought any medical advice. She did not have any history of relevant medication & substance abuse. All family members are healthy and alive except one of her paternal uncle had stroke 3 months back at the age of 55. Physical examination reveals good nutrition with normal peripheral pulses but absent right radial & brachial pulse. Her blood pressure is normal with no carotid, supraclavicular or renal bruit. Her neurological examination reveals left sided upper motor neuron type facial palsy. Tone is increased on the left side with diminished muscle power (MRC Grade o). All deep tendon reflexes are exaggerated on left side with left plantar extensor. Gait is hemiplegic.

Investigations regarding- CT scan of brain done immediately after admission into hospital shows Infarction of right temporoparietal region that is right MCA territory and bilateral cervical rib on chest X-ray. Subsequent MRI and MRA revealed infarction of right MCA with normal posterior circulation.

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Duplex study neck vessels is normal .Duplex study territory of upper right arm vessels- shows Short right brachial artery with suspected early bifurcation at the level of mid-arm. Non-detectable right radial artery .Digital Subtraction Angiography (DSA) is done after 2 months shows normal cerebral angiogram with normal right common carotid artery and its bifurcation and left common carotid and left subclavian artery angiography are normal . There is an obstruction of right subclavian artery with superadded thrombus just after where clavicle and first rib crosses each other. Multiple tandem obstruction is seen shortly thereafter and right axillary artery is very narrow calibered and totally occluded just above elbow. It is reformed from collaterals below the elbow and divides into normal looking radial and ulnar branches where distal flow is poor. Transthoracic echocardiography, thrombophilia screen, and C-reactive protein were normal. A screen for arrhythmias was negative. However the test for anti ds DNA, anticardolipin antibody. antiphospholipid antibody , protein C, protein S all are negative. p-ANCA, c-ANCA and S homocysteine are normal.

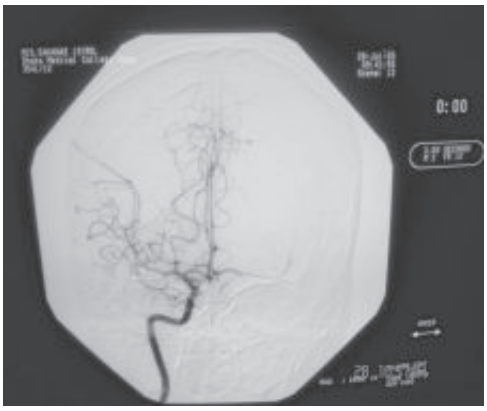

Fig.-1: *RICA angiogram, AP view shows Normal Intracranial circulation*

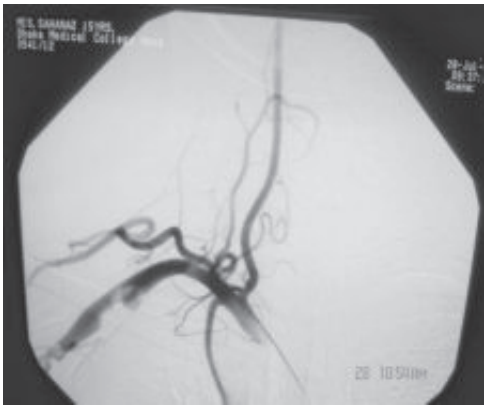

Fig.-2: *Right subclavian artery angiogram shows normal vertebral ostium .There is an obstruction with superadded thrombus just after where clavicle and first rib crosses each other. There is multiple tandem obstruction shortly there after*

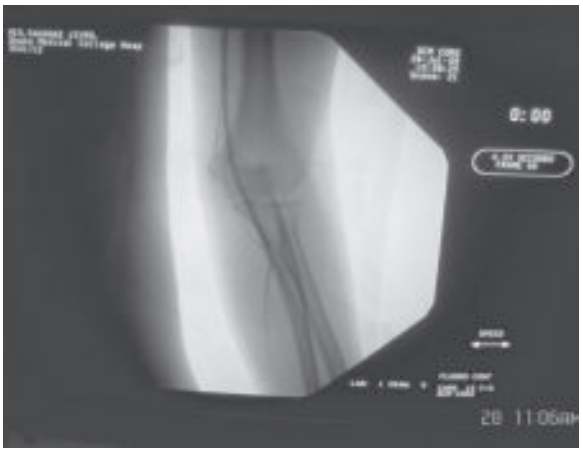

Fig.-3: *Right axillary artery angiogram shows very narrow caliber and finally total occlusion just above elbow. It is reformed from collateral below the elbow and divides into normal looking radial and ulnar branches where distal flow is poor.*

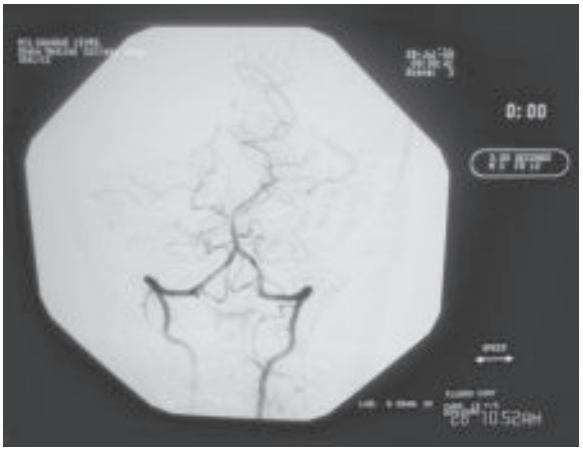

Fig.-4: *Vertebral artery angiogram. AP view shows normal intracranial circulation*

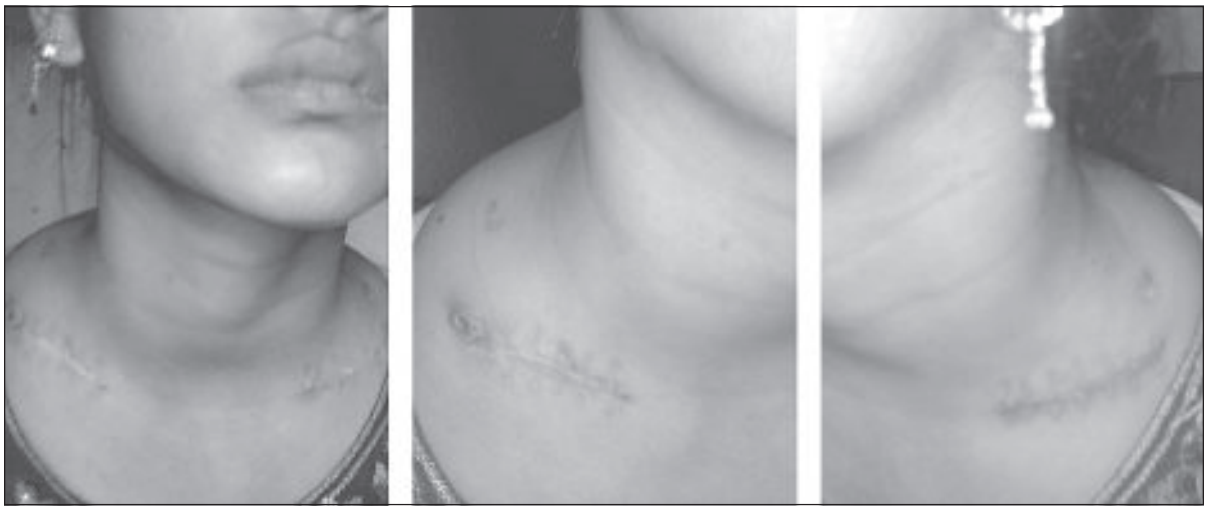

Fig 5: *surgical intervention 0f TOS in our patient - supraclavicular approach.*

Discussion:

The abrupt onset of left hemiparesis with focal convulsion in this patient suggested ischemic stroke involving right temporoparietal region which was confirmed by CT scan [2] .The commonest cause of ischemic stroke in a young patient is embolism, originating from the heart[3]. However, clinical evaluation, normal electrocardiographic assessment, and a negative transthoracic echocardiogram made the heart an unlikely source of embolism in this patient. Less commonly, artery-to-artery embolism, especially from the proximal circulation and often secondary to dissection, is an important cause of stroke in the young[3]. Free flow of contrast in the proximal vessels, including the cervical vertebral artery and innominate artery, made embolism from the proximal vessels unlikely. X-ray cervical spine suggested a right cervical rib causing thoracic outlet syndrome (TOS) and distal subclavian artery disease. There are 2 possible mechanisms of cerebral embolism in this case: retrograde propagation of a thrombus and retrograde cerebral embolism. The subclavian artery may be subject to trauma by a cervical rib, resulting in progressive stenosis and occlusion. Typically, there may be poststenotic dilation and aneurysm formation. A mural thrombus may form at the site of the compression or in the aneurysmal segment. A thrombus thus formed has an opportunity of extending proximally and embolizing via the right common carotid artery to occlude right middle cerebral artery (in this patient). Retrograde propagation of a thrombus has been described[4].

Theoretically subclavian artery flow patterns measured using doppler ultrasound indicated both antegrade and retrograde flow occurring across both subclavian lumina in cardiac systole with small amounts of retrograde flow in diastole. Retrograde flow in diastole was greater in the occluded subclavian artery compared to the left. It was noted that retrograde flow increased on extreme rotation of the neck. Retrograde flow could carry an embolus toward the origin of the vertebral artery, and the next cardiac contraction would propel the embolus into the vertebral circulation. Previous case reports have demonstrated bidirectional flow in normal as well as occluded subclavian arteries[5]. These too have demonstrated greater retrograde flow in the occluded vessels suggesting greater reverse flow due to increased peripheral resistance. TOS refers to compression of the neurovascular structures in the area just above the first rib and behind the clavicle. The subclavian artery is affected in 1% of cases of TOS. Cervical ribs and the first anomalous rib are rare conditions, present in approximately 1% of the population and in 4.5% of patients with TOS[6].

The type of cervical rib is of significance in arterial complications[7].It has been established that short and incomplete ribs preferentially produce neurologic complications by nerve compression, while long or complete ribs as seen in this patient have arterial complications. Thromboembolism to the forearm and digits is the most typical clinical presentation of patients with distal subclavian artery

disease due to TOS. Due to collateral formation, ischemic symptoms may be mild or absent. The presence of collaterals also suggests longstanding thrombosis of the distal subclavian artery.

Previous case reports have described distal subclavian artery disease secondary to TOS causing cerebral embolism[8]. The majority of these cases described right TOS leading to cerebral embolism, involving commonly the right middle cerebral artery. This phenomenon is possibly due to the anatomic characteristics of the right carotid artery branching from the brachiocephalic artery and the differences in caliber of the common carotid and vertebral arteries with reduced resistance seen in the larger common carotid artery.

Surgical intervention is indicated in vascular TOS as it is typically resistant to conservative management. The surgical treatment of arterial TOS includes the excision of the cervical and/or first rib, followed by reconstructive vascular procedure, such as resection and anastomosis or replacement with vein or prosthetic grafts[9]. Two common approaches to TOS are the supraclavicular and transaxillary approaches. The advantage of the supraclavicular approach is that it allows good exposure of the brachial plexus, medial two thirds of the first rib, and the cervical rib, if present. As a result, first rib resection or anterior and middle scalenectomies can be done with this approach. In our patient surgeons preferred the supraclavicular approach.

The success rates of the supraclavicular and transaxillary approaches defined as complete to partial resolution of symptoms are 87.5% to 89%and 81% to 93%, respectively[10]. Potential complications from TOS decompression surgeries include major neurovascular injuries, Horner's syndrome and phrenic nerve, long thoracic nerve, supraclavicular nerve, and intercostal brachial nerve injuries[11].

Surgical treatment may be considered in a patient with occlusive distal subclavian artery disease secondary to a cervical rib in order to prevent recurrent embolism[12].

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