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CONTENTS

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Bangladesh Journal of Neuroscience 2012; Vol. 28 (2) : 67-73

ORIGINAL ARTICLES

Duplex Study of Carotid Artery in Patients with Ischemic Stroke

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Abstract

Objective: *To determine the frequency and characteristics of carotid artery stenosis in acute ischemic stroke patients and to assess the significance of common risk factors for carotid stenosis in these patients.* ***Method:*** *It was cross-sectional observational study which was carried out in neurology department of Bangabandhu Sheikh Mujib Medical University (BSMMU) during the period of January 2010 to December 2011 and one hundred patients admitted with acute ischemic stroke were included in the study. Doppler ultrasound was performed during hospitalization to find out carotid artery stenosis. Statistics analysis was done with SPSS - 14.* ***Results:*** *Out of one hundred (100) patients, eighty (80%) were males and twenty were (20%) were females. The patients were dividing into two groups with and without carotid stenosis. Less than 50% carotid artery stenosis (insignificant stenosis) was seen in 40 %(n=40) cases and significant stenosis was seen in 60% (n=60) patients. Overall 86% (n= 46) out of 60 patients were found to have carotid artery stenosis on the ipsilateral side corresponding to the ischemic lesion and 19% (n=11) had stenosis on the contralateral side. Out of significant stenosis ,mild (50% stenosis) in 12% (n=7) patients, moderate (51-69%) stenosis in 50%(n= 30) patients and severe (>70%) stenosis in twenty (n=33%) patients . Near total occlusion was seen in three (5%) patients. The presence of stenosis was significantly correlated with older age and the presence of multiple risk factors.* ***Conclusion:*** *Carotid artery stenosis is strongly associated with ischemic stroke. Doppler studies are recommended for the high risk patients for the primary as well as secondary prevention of ischemic stroke.*

Key word: *Duplex study, Carotid artery, Ischemic stroke*

Abbreviations: *CAS (carotid artery stenosis) , ICA (internal carotid artery)*

Introduction:

Stroke is the most common life-threatening neurological disorder and the most important single cause of disability. According to World Health Organization estimates for the year 2020, stroke will stay as the second leading cause of death along with Ischaemic heart disease, both in developing as well as developed countries[1]. During the last three decades there is a decline in the incidence of the disease in the Western population while the burden of the disease in South Asian countries (India, Pakistan, Bangladesh and Sri Lanka) has inclined and is expected to rise further[2]. In Pakistan estimated stroke incidence is close to 250 per 100,000 populations, which means that there are 350,000 new stroke patients every year in the country[3].

Clinically stroke is the result of a disturbance of cerebral circulation, either due to occlusion of main blood vessel due to thrombo-embolism or rupture of a blood vessel. About 85% of all strokes are of ischaemic origin; caused by thrombotic or embolic blockage of a cerebral artery[4].

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Multiple risk factors are associated with Stroke. The Non-modifiable risk factors are age, sex, family history, race and ethnicity and the modifiable risk factors include hypertension, cardiac disease, diabetes mellitus hyperlipidaemia, cigarette smoking, alcohol abuse, physical inactivity, carotid stenosis, and transient ischaemic attack[5]. Carotid artery stenosis (CAS) is a major risk factor for stroke and for the symptomatic cerebrovascular disease. Approximately 20-30% of all ischemic strokes are caused by carotid occlusive disease[6].

Current techniques for the assessment of carotid artery disease includes color Doppler Ultrasound, Digital Subtraction Angiography, Magnetic Resonance angiography and computed resonance angiography. Duplex ultrasonography is currently the principal and undoubtedly the most accurate non-invasive diagnostic modality available for evaluation of carotid artery stenosis. It provides information about the degree of carotid stenosis, the velocity and character of blood flow and plaque morphology[7]. Grading of carotid artery stenosis was done according to radiological society of consensus 2008[8]. Screening of carotid by duplex ultrasound is recommended for the high risk patient to find out the presence of carotid stenosis in order to plan out medical and surgical intervention for primary as well as secondary prevention of cardiovascular events.

Patients and Methods:

This cross sectional observational study which was carried out on one hundred (100) consecutive patients with acute ischemic stroke admitted in the Department of Neurology, BSMMU, Dhaka .The patients included were of both sexes and age above 18 years.

Patients having history of head injury, evidence of intracranial hemorrhage or space occupying lesion on computed tomographic scan of brain, patients who recovered from neurological deficit within 24 hours, patients having signs and symptoms of posterior circulation infarct and patients having signs of meningeal irritation were excluded from the study. Doppler ultrasound was performed during the hospitalization in all those patients with Siemens Acuson Antares 10MHz linear transducer, who fulfilled the inclusion criteria. The risk factors were evaluated by history, physical examination, electrocardiogram and laboratory investigations during hospitalization. These included age, sex, hypertension, diabetes mellitus, hyperlipidaemia smoking and Ischemic heart disease. Acute ischemic stroke was defined as focal neurological deficit of sudden onset lasting for >24 hours with evidence of cerebral infarction or a normal CT scan of brain without evidence of hemorrhage. Hypertension was conveniently defined for the study purpose as a systolic blood pressure (SBP) of > 180 mmHg or a diastolic blood pressure (DBP) > 100 mmHg on admission or a SBP of > 140 mm Hg and or DBP > 90 mm Hg, seventy two hours after admission. Patients previously known to be hypertensive by history or those who were on anti hypertensive medication were also included. Diabetes mellitus was considered when subjects gave history of diabetes mellitus and/or were on oral hypoglycemic drugs or insulin treatment or had random blood sugar > 200mg on two occasions during the hospital stay. Coronary artery disease (CHD) was considered if the patient had a recent or past history of myocardial infarction, was on anti angina drugs, or had typical ECG findings of recent / previous ischaemic events. The patients having non specific ST segment and/or T wave changes were not included in this analysis.

A smoker was conveniently defined as a person who smoked at least one cigarette per day for the preceding three months or more or was using tobacco in any form.

Hyperlipidaemia was conveniently defined when a patient had a previous diagnosis of it and/or was on lipid lowering agents or had fasting serum cholesterol of > 200mg, seventy two hours after admission in the hospital.

Statistical package for social sciences (SPSS-14) was used to analyze data. Qualitative variables were analyzed by finding their frequencies and percentages. Chi-square test was used to check proportion difference between patients with and without carotid artery stenosis, for gender, age groups and risk factors. P value 0.05 was considered level of significance.

Results:

Out of one hundred (100) patients, eighty (80%) were males and twenty (20%) were females (Table-I). The patients were divided into two groups with and without carotid stenosis. Less than 50% carotid artery stenosis (insignificant stenosis) was seen in 40 %(n=40) cases and significant stenosis was seen in 60% (n=60) patients(Table-I).. Overall 86% (n= 46) out of 60 patients were found to have carotid artery stenosis on the ipsilateral side corresponding to the ischemic lesion. Another 19% (n=11) had stenosis on the contralateral side (Table-I). Distribution of degree of stenosis was mild (50% stenosis) in 12% (n=7) of patients, moderate (51-69%) stenosis in 50%(n= 30) of patients and severe (>70%) stenosis in twenty (n=33%) of patients and near total occlusion were seen in three (5%) patients(Table-II). The presence of stenosis was significantly correlated with older age and the presence of multiple risk factors. Risk factors associated with carotid artery stenosis either alone or in combination, its relation with degree of stenosis and comparison with patients without stenosis was shown in Table III. Degree of carotid artery stenosis was mild in nine lesions (18%), moderate in fifteen lesions (30%), severe in twenty one lesions (42%) and critical in five lesions (10%) .On ipsilateral side, homogenous plaque was found in twenty three patients (59%), heterogeneous in fourteen (35.9%), and thrombosed in two patients (5.1%) only table-IV. Images of various types of carotid plaques are shown in Fig. 1-4.

Table-I

Summation of study result

Total No of patients: 100	Significant carotid artery stenosis : 60% (n=60)
	Insignificant carotid artery stenosis : 40% (n=40)
Male: 80(80%)	
Female: 20(20%)	Ipsilateral stenosis 81% (n= 49)
	Contra lateral stenosis 19% (n= 11)

Table-II

Distribution of different significant carotid artery stenosis : 60% (n=60)

PSV of ICA/CCA ratio	Number with %
2 (50% stenosis in ICA)	N=7 (12%)
2-4(51-69% stenosis in ICA)	N=30(50%)
>4 (>70% stenosis in ICA)	N= 20(33%)
Near total occlusion	N= 03(05%)

Table-III

Risk factors and degree of stenosis in ICA (total patients with stenosis n=60)

	PSV ratio of ICA/CCA =2 (50% stenosis)	PSV ratio of ICA/CCA =2-4 (51-69% stenosis)	PSV ratio of ICA/CCA =>4 (>70% stenosis)	Total N=60
Single risk factor	02	04	01	7(12%)
Two risk factors		15	05	20(33%)
Three or more risk factor		25	08	33(55%)

Table-IV

Plaque morphology

Plaque morphology (sonographicaly)	Number and %
Homogenous plaque	Number of patients =35 (58%)
Heterogeneous plaque	Number of patients =12 (20%)
Calcified plaque	Number of patients = 10(17%)
Ulcerated plaque	Number of patients = 03(05%)

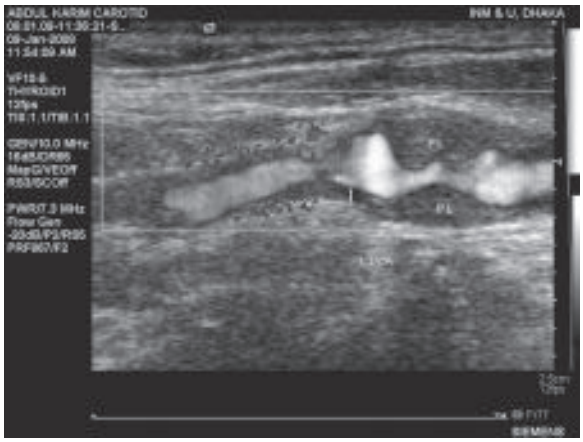

Fig.-1 : *Hypoechoic plaque in color Doppler*

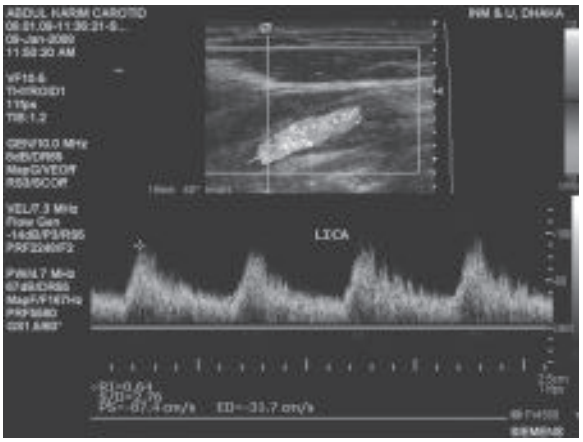

Fig.-2: *Doppler spectrum in LICA*

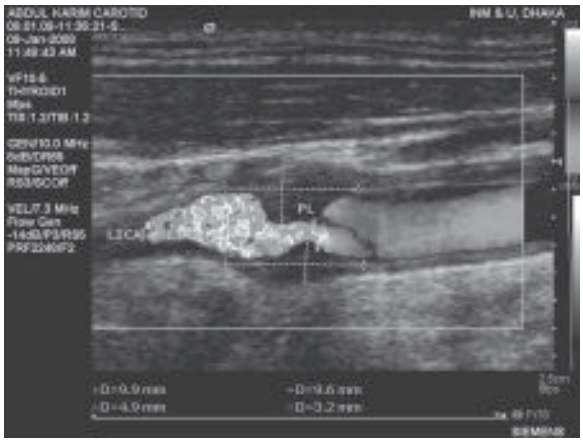

Fig.-3: *Heterogeneous plaque in bulb of LICA*

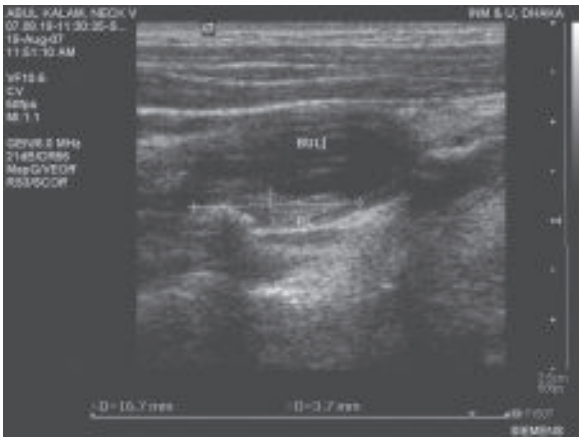

Fig.-4: *Heterogeneous plaque in bulb of LICA*

Discussion:

Large multicenter prospective studies such as North American Symptomatic Carotid Endartectomy Trial (NASCET) and European Symptomatic Trial (EST) have shown the etiological significance of carotid lesions in ischemic stroke patients[9]. The risk of ischemic stroke increases with the degree of carotid stenosis[10]. Because patients with symptomatic occlusion of the internal carotid artery (ICA) and compromised cerebral blood flow are at risk for future ischemic infarcts therefore early identification and accurate determination of the degree of carotid artery stenosis is useful in risk-factor management, with appropriate medical or surgical intervention[11].

The frequency of Carotid Artery Stenosis (CAS) was 39% in this study, as compared to 44% by Laeeq Ahmed[12] and 48.5% by Mozzam Ali[13].However another local study conducted by Khan et al found CAS in only 18.18% of patients[14] but this study included only those patients who had stenosis of greater than 70%. The lower figures (8%) were also noted by Tan[15] from Taiwan and by Alexandrore et al [16] who reported stenosis of equal or greater than 70% in 17% of 348 patients.

We also evaluated the presence of well known common risk factors in our patient population and compared these risk factors in patients with and without carotid artery stenosis. Advanced age, male gender, hypertension smoking, Ischaemic heart disease and hyperlipidaemia significantly contributed to the presence of atherosclerotic plaque, but in majority of cases more than one risk factor was involved in both in the frequency as well as the severity of carotid artery stenosis.

Older age is an important and well known risk factor for the development of Carotid artery atherosclerosis. In our study the majority (56%) of patients with stroke were older than 60 years and when we compared this age subgroup having carotid stenosis (28/39) to the patients having no stenosis (28/61) , the difference was statistically significant ($P < 0.010$). All three patients of more than 80 years had carotid stenosis. These findings were consistent with certain international studies. An Indian study by Sethi et al[17] found that mean age of patients with carotid lesion was 60.03 years as compared to 48.83 years in patients without any carotid lesion. Kerenyi[18] also noted that mean age of the patient with CAS was 66.9 ± 12.8 years.The majority of our patients with carotid artery stenosis were male but this gender difference was found to be not significant ($P < 0.442$).Hypertension was the most common risk factor present in 76.92% of cases either as a single risk factor or associated with other risk factors Elevated systolic blood pressure accelerates the progression of intima medial thickness (IMT) in the carotid artery, however isolated hypertension occurs in only less than 20% of patients with stroke and is usually associated with other risk factors that is why antihypertensive treatment alone may fail to prevent stroke[19,20]. Smoking is widely accepted as one of the important risk factor for ischaemic stroke in western countries, and is associated with the progression of carotid plaques[18]. Smoking is associated with raised fibrinogen levels, increased packed cell volume, and decreased macrophage activity changes in lipid biochemistry. Smoking increases arterial wall stiffness and alters the pattern of arterial blood flow[19-21]. In our study smoking was present in 43.59% cases. However an independent association of smoking with carotid artery stenosis could not be confirmed as nearly all the smokers had at least one other risk factor, mainly hypertension. Atherosclerosis is presumed to be accelerated in diabetes for a number of reasons. First, diabetes is associated with an increased risk of traditional coronary heart disease (CHD) risk factors, including hypertension, dyslipidaemia, obesity, and hyperinsulinaemia, other metabolic disturbances unique to diabetes, such as increased levels of circulating glucose, advanced glycation end products, and oxidation of lipoproteins might also increase the risk and rate of atherosclerosis[22]. Interestingly Diabetes was found to be less common as compared to patients without stenosis in our study.

Higher LDL cholesterol levels are associated with higher incidence of carotid atherosclerotic disease while high levels of HDL cholesterol have protective role[19]. In the present study hyperlipidaemia in ischaemic stroke patients having carotid artery stenosis was 25.64%.

In our study very significant number (43%) of patients with CAS had Ischaemic heart disease ($P < 0.0001$). A local study conducted by Khan et al[23] showed that 25% of patients with coronary artery disease had carotid artery stenosis of more than 50% while overall about 94% of patients had some evidence of plaque. In Japanese patients who underwent coronary artery bypass grafting (CABG) because of severe coronary artery disease, a high incidence of carotid stenosis was noted[23].

The role of calcification in atherosclerotic disease with regard to clinical symptoms has been studied in pathologic and sonographic studies. Calcium is postulated to give stability by stiffening the plaque resulting in protection against biomechanical stress

and subsequent disruption thus preventing cerebrovascular events. Most studies favour that plaque having high contents of calcium and fibrous tissues are less symptomatic than non-calcified lipid rich plaque or thrombosed plaque. Nandalur et al[22] found that calcified plaques were 21 times less likely to be symptomatic than noncalcified plaques. In our study similar trends were found and majority (59%) of our stroke patients having carotid artery stenosis had non calcified plaques (shown in Fig. 1-4).

Limitations:

The present study has some limitations. As this study was a single hospital-based study conducted on patients having a different clinical and risk factor profile, these results cannot be applied to the general population.

Conclusions and Recommendations:

The Carotid Artery Stenosis is a well known risk factor for the development of the ischaemic stroke and a significant number of patients in our study were found to have stenosis. The present study shows that the combined presence of multiple risk factors like age, hypertension, smoking and ischaemic heart disease is strongly associated with carotid artery stenosis. High risk patients should be screened by Doppler ultrasonography for the presence of carotid stenosis in order to plan out medical and surgical intervention for the primary as well as secondary prevention of cerebrovascular events.

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Bangladesh Journal of Neuroscience 2012; Vol. 28 (2) : 74-80

Association of Serum Folic Acid with Ischemic Stroke

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Abstract:

Background: *Stroke is the third commonest cause of death in developed countries and is responsible for the physical disability of a large population. The study was designed to see the association of serum folic acid with ischemic stroke. It was concluded that the low levels of folic acid are associated with ischemic stroke.* ***Aim and objectives:*** *To evaluate the association of serum folic acid level with ischemic stroke and to measure and compare the serum folic acid level among the cases and control subjects.* ***Material and method:*** *This study was a case-control study which was conducted in the Department of Neurology and Department of Biochemistry of BSMMU, Dhaka, between the period of 1st January 2010 and 31st December 2011 for duration of two years. A total number of 60 patients presented with ischemic stroke and 60 control person were enrolled in this study. All patients of both sexes, aged between 20 years and above presented with ischemic stroke, from 0 day to 1 month that was confirmed by CT scan of head/MRI of brain. Blood sample was collected from the cases and the controls and analyzed at the Dept. of Biochemistry, BSMMU for estimation of serum folic acid, serum homocysteine fasting blood sugar. Fasting lipid profile for cases only.* ***Result:*** *The mean ± SD of age of the cases was 58.42 ± 11.47 and among the cases 45 (75.0%) were male and 15 (25.0%) were female. Among the control male and female were 43 (71.7%) and 17 (28.3%) respectively. The mean (±SD) serum folate level of case and control group was 6.26(± 4.06) and 8.07(± 4.70) respectively. Statistically significant differences was observed between case and control group in term of Serum folate (p<0.05). This study showed serum folate level was deficient at the early period of ischemic stroke.* ***Conclusion:*** *Low serum folate concentration is significantly and independently associated with increased risk for ischemic stroke.*

Introduction:

Stroke is defined by World Health Organization (WHO) as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer, or leading to death, with no apparent cause other than of non-traumatic vascular origin[1].Stroke is the third most common cause of death in the developed world after heart disease and cancer, after the age of 40 and is the most common cause of adult physical disability[2]. Prevalence of stroke in Bangladesh is 0.30%, and the ratio of male: female patient's was 3.44:2.41[3]. It poses a major socio-economic challenge in the occupational and neuro-rehabilitational programmes for survivors[4].

Among numerous risk factors for stroke, only two-thirds of all strokes can be attributed to known causal risk factors. One of them is elevated plasma homocysteine concentration resulting from its metabolic enzyme deficiencies or deficiencies of vitamin B_6, B_{12} and folic acid[1]. Approximately two-thirds of the cases of elevated homocysteine have

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been estimated to be due to low or moderate concentrations of these vitamins of which folic acid is considered the most important[5]. A number of epidemiological studies have linked folate deficiency and resultant elevated plasma total homocysteine levels with an increased risk of cardiovascular disease and ischemic stroke[6-10].

The best-known beneficial action of FA is its homocysteine lowering effect. Being a cofactor in 1-carbon metabolism, folate promotes the remethylation of homocysteine which is reconverted to methionine by methionine synthase and to cystathionine and subsequently to cysteine, which is excreted in the urine or incorporated into glutathionine[7].Our study were designed to evaluate the association of serum folic acid level with ischemic stroke and to measure and compare the serum folic acid level among the cases and control subjects.

Materials and Methods:

This was a case-control study carried out in Department of Neurology of BSMMU, Dhaka, from 1st January 2010 and 31st December 2011.

Cases were selected following the inclusion and exclusion criteria-

A. Inclusion Criteria
   1. All patients of ischemic stroke, confirmed by CT scan of head/MRI of brain from 0 day to 1 month.
   2. Patients with ischemic stroke of both sexes.
   3. Patients with ischemic stroke of 20 years of age & above.

B. Exclusion Criteria
   1. Patients of stroke from haemorrhage, venous thrombosis.
   2. Severely ill patients.
   3. Patients or attendants unwilling to take part in the study.
   4. Those who are taking the following drugs- Anti epileptic, Anti metabolites- methotrexate, Cholestyramine, Penicillamine, OCP, Multivitamins containing Folic Acid.
   5. Patients presented with AF, IHD (within 6 weeks of acute stroke), prosthetic heart valve and endocarditis.

Controls were selected following the inclusion and exclusion criteria-

Inclusion criteria

1. Age and sex group matched with the cases.
2. Other than ischemic stroke patient, persons willing to take part in the study.

Exclusion criteria

1. Those unwilling to take part in the study.
2. Having overt cardiovascular disease
3. Confounders of low serum folic acid level already described earlier.

Data were collected in a structured questionnaire at stroke clinic and neurology ward in BSMMU. Collection of blood sample & estimation of serum folic acid, homocysteine, fasting blood sugar, lipid profile from the cases and the controls were done at the department of Biochemistry, BSMMU.

Result:

A total number of 60 patients of ischemic stroke as case and 60 persons as control were enrolled in this study. The results of the present study as follows:

Table-I

Distribution of the respondents by age (n=120)

Age	Group		p value
	Case	Control	
20 - 29	1 (1.7)	3 (5.0)	
30 - 39	3 (5.0)	4 (6.7)	
40 - 49	6 (10.0)	10 (16.7)	
50 - 59	22 (36.7)	20 (33.3)	
60 - 69	14 (23.3)	11 (18.3)	
70 and above	14 (23.3)	12 (20.0)	
Total	60 (100.0)	60 (100.0)	
Mean ± SD	58.42 ± 11.47	54.17 ± 13.97	0.071*

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

Table 1, shows the distribution of the respondents by age. Mean ± SD of age of the cases was 58.42

± 11.47 years. Among the cases most common age group was 50 to 59 years (36.7%) followed by 60 to 69 and 70 and above (23.3%). Mean ± SD of age of the control was 54.17 ± 13.97 years. Among the control most common age group was 50 to 59 years (33.3%) followed by in the age group of 70 years and above (20.0%). There is statistically no significant difference in age between the case and control (p>0.05).

Table-II

Distribution of the respondents by sex (n=120)

Sex	Group		p value
	Case	Control	
Male	45 (75.0)#	43 (71.7)	0.680*
Female	15 (25.0)	17 (28.3)	
Total	60 (100.0)	60 (100.0)	

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

Table II, shows the distribution of the respondents by sex. Among the cases 45 (75.0%) were male and 15 (25.0%) were female. Among the control male and female were 43 (71.7%) and 17 (28.3%) respectively. There is no statistically significant (p>0.05) difference in sex between the case and control.

Table-III

Distribution of the respondents by history of smoking (n=120)

History of smoking	Group		p value
	Case	Control	
Present	40 (66.7)#	19 (31.7)	0.001*
Absent	20 (33.3)	41(68.3)	
Total	60 (100.0)	60 (100.0)	
If yes, pack year			
Mean ± SD	4.90 ± 2.28	3.88 ± 1.32	
(Min -Max)	(2-10)	(2-6)	

*Chi-square test was done to measure the level of significance.
#Figure within parentheses indicates in percentage.
Odd ratio (95%CI) = 4.32 (2.01- 9.27)

Table III, shows the distribution of the respondents by history of smoking. Among the cases 40 (66.7%) were smoker and 20 (33.3%) were non smoker. Among the control 19 (31.7%) were smoker and 41(68.3%) were non smoker. Mean ± SD of pack year among case and control was 4.90 ± 2.28 and 3.88 ± 1.32 respectively. There is statistically significant difference in history of smoking between the case and control (p<0.05).

Table-IV

Distribution of the respondents by hypertension (n=120)

Hypertension	Group		p value
	Case	Control	
Present	48(80.0)#	07(11.7)	0.001*
Absent	12(20.0)	53(88.3)	
Total	60 (100.0)	60 (100.0)	

*Chi-square test was done to measure the level of significance.
#Figure within parentheses indicates in percentage.
Odd ratio (95%CI) = 30.28 (11.02-83.207)

Table IV shows the distribution of the respondents by hypertension. Among the cases 48(80.0%) were hypertensive and 12(20.0%) had normal blood pressure. Among the control 7(11.7%) were hypertensive and 53(88.3%) were normotensive. There is statistically significant difference in hypertension prevalence between the case and control (p<0.05).

Table-V

Distribution of the respondents by Diabetes Mellitus (n=120)

Diabetes Mellitus	Group		p value
	Case	Control	
Present	02 (03.3)#	02 (03.3)	1.000*
Absent	58 (96.7)	58 (96.7)	
Total	60 (100.0)	60 (100.0)	

*Chi-square test was done to measure the level of significance.
#Figure within parentheses indicates in percentage.
Odd ratio (95%CI) = 1.00 (0.14 - 7.34)

Table V, shows the distribution of the respondents by diabetes mellitus. Among the cases 2 (3.3%) were diabetic and 58 (96.7%) were non diabetic. Among the control 2 (3.3%) were diabetic and 58 (96.7%) were non diabetic. There is statistically no significant difference in diabetes prevalence between the case and control (p>0.05).

Table-VI

Serum folate and homocystein level among cases (n=60) and controls (n=60)

Laboratory findings	Group		p value*
	Case	Control	
Serum folate (ng/ml)	6.26 ± 4.06 (1.83 - 18.98)	8.07 ± 4.70 (1.20- 20.98)	0.025
Serum homocysteine (μmol/L)	19.05 ± 11.60 (5.71 - 59.00)	17.46 ± 9.94 (5.71- 50.00)	0.422

*t test was done to calculate the level of significance.

Table VI, shows mean (±SD) serum folate level of case and control group was 6.26 (± 4.06) and 8.07 (± 4.70) respectively. Statistically significant differences of serum folate level was observed between case and control group ($p<0.05$). Mean (±SD) Serum homocysteine level of case and control group was 19.05(± 11.60) and 17.46(± 9.94) respectively. Serum homocysteine level did not show statistically significant differences ($p>0.05$) between case and control group.

Discussion:

Age is the single most important risk factor for stroke. In this study the mean ± SD of age of the cases was 58.42 ± 11.47 years, minimum 28 and maximum 80 years. Most common age group of cases was 50 to 59 years (36.7%) followed by 60 to 69 and 70 and above (23.3%). Maximum patients of this study were above 46 years. In 1990 Biller J et al[11] studied 51 stroke patients majority of them being in the 50-69 age groups. Other age group of cases was 40 – 49 years (10.0%), 30 to 39 years (5.0%) and 20 – 29 years (1.7%). Mean ± SD of age of the control was 54.17 ± 13.97 years with median (52.50) and maximum 86 and minimum 21 years. Among the control most common age group was 50 to 59 years (33.3%) followed by in the age group of 70 years and above (20.0%). Other age group in control were 20 to 29 years (5.0%). 30 to 39 years (6.7%), 40 to 49 years (16.7%), 60 to 69 (18.3%) years. There was statistically no significant difference in age between the case and control ($p>0.05$) (Table 1). The older the person is, the greater the risk for stroke[12]. For each successive 10 years after age 55, the stroke rate rises more than doubles in both men and women[13]. Present study revealed that middle and old age people are prone to stroke than the younger group. American Heart Association (AHA) revealed the same fact on 2006 that the older are at the greater risk for stroke[12]. In 2000 Basharat et al. showed that the mean age was 53.0 years for all cases of stroke while mean age in males and females was 56.2 and 48.9 years respectively[14]. This study also shows that the incidence of stroke rises with the increase of age. Similar observation were obtained by Hayee et al.[12], Banford et al.[15] and Arif et al.[16].

Among the cases 45 (75.0%) were male and 15 (25.0%) were female. Among the control male and female were 43 (71.7%) and 17 (28.3%) respectively. There is no statistically significant difference in sex between the case and control ($p>0.05$) (Table 2). In 1998 Feigin et al. and Basharat et al. in 2000 found that male was attacked by stroke more than female[14,17]. In Bangladesh, few hospital based studies revealed the male dominant picture [12,18,19]. But Cull et al (1995) concluded that in underdeveloped countries females are given less priority in all respect including hospital admission and treatment for illness[20].

Among the cases 40 (66.7%) were smoker and 20 (33.3%) were non smoker. Among the control 19 (31.7%) were smoker and 41(68.3%) were non smoker. Mean ± SD of pack year among case and control was 4.90 ± 2.28 and 3.88 ± 1.32 respectively. There is statistically significant difference in history of smoking between the case and control ($p<0.05$). In one study Jalal Uddin in 2007 found smokers having a risk of ischaemic stroke 1.084 times higher than those of non-smokers[21]. Somay et al. obtained similar result in

their study[22]. In a case-control study Khan, found that 55% of ischaemic stroke patients were smoker where only 33% were smoker in control group[19].

Among the cases 48(80.0%) were hypertensive and 12(20.0%) were not. Among the control 7(11.7%) were hypertensive and 53(88.3%) were not. There is statistically significant difference in hypertension between the case and control ($p<0.05$). Higher prevalence of hypertension in ischaemic stroke patients was also observed by Somay et al[22]. Similar results were obtained by Jalal Uddin, Hannan and Khan [18,19,21]. In analysis of risk factors of stroke Carrieri noted hypertension was present in 52.11% of stroke patients[23]. All these findings are consistent with the result of the present study.

Among the cases 2 (3.3%) were diabetic and 58 (96.7%) were non diabetic. Among the control 2 (3.3%) were diabetic and 58 (96.7%) were non diabetic which showed no significant difference between the case and control ($p>0.05$). Earlier case-control study found 33% of the ischemic stroke patient had diabetes while 13% of the controls were diabetic and diabetes was established as a risk factor for ischemic stroke. The findings of present study are inconsistent with previous studies as this is a hospital base study.

In 1995 Giles et al.noted that folate concentration <9.2 nmol/L may be a risk factor for ischemic stroke especially in blacks[24]. Increased folate intake is associated with decreased risk of ischemic stroke in men[25]. But in other studies inconsistency was noted with serum folate or folate intake in relation to incidence of stroke[26-28].

Mean (±SD) serum folate level of case and control group were 6.26 (± 4.06) and 8.07(± 4.70) respectively which showed significant differences between case and control group ($p<0.05$). Mean (±SD) serum homocysteine level of case and control group were 19.05(± 11.60) and 17.46(± 9.94) respectively and did not show statistically significant differences between case and control group ($p>0.05$). Homocysteine levels depend in part on folate status, lower folate levels lead to higher homocysteine levels[29]. As a result of the observed inverse association between homocysteine levels and stroke, folate has been hypothesized to be protective against stroke incidence[30] . Folate is required for the remethylation of homocysteine to methionine, which in turn reduces the concentration of homocysteine available to support oxidative stress. Giles et al (1995) investigated whether a folate concentration <9.2 nmol/L was associated with ischemic stroke in a national cohort. They noticed that after adjusting for age, race, sex, education, diabetes, history of heart disease, systolic blood pressure, body mass index, hemoglobin level, cigarette smoking, and alcohol intake, participants with a folate concentration <9.2 nmol/L were at slightly increased risk for ischemic stroke (relative risk [RR], 1.37; 95% confidence interval [CI], 0.82 to 2.29)[24]. There was a folate-race interaction (*P*=.11 for interaction term). Whites with a folate concentration <9.2 nmol/L had a relative risk of 1.18 (95% CI, 0.67 to 2.08), whereas blacks had a relative risk of 3.60 (95% CI, 1.02 to 12.71). In 2010 *Kirtania* et al in a case control study showed that the mean folic acid levels in case group and control group were 2.29±0.54 ng/ml and 7.24±2.19 ng/ml respectively. They suggest**ed** that low levels of serum vitamin B_{12} and folic acid are associated with ischaemic stroke[31].

Conclusion:

Low serum folate concentration is significantly and independently associated with increased risk for ischemic stroke. Serum homocysteine concentration appears insignificant as risk for ischemic stroke. Further studies are required to establish these associations in our ethnic population. As the present study conducted in a single center in Dhaka city with small sample size, to find out such potential risk factors, more study is needed to establish that the low serum folate as a risk for ischemic stroke in Bangladeshi population.

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Sodium Valproate is More Effective than Pizotifen in the Prophylaxis of Migraine Patients

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Abstract:

Background and objectives: *Migraine is now ranked as number 19 among all diseases causing disability by WHO[1] which is characterized by recurrent attacks of various combinations of headache and neurological, gastrointestinal and autonomic symptoms[2] accompanied by photophobia, phonophobia and vomiting[3]. The treatment of migraine involves acute, preventive drugs and non-pharmacological strategies. The basic principle in management of migraine is avoiding the trigger factors, blocking the mediators and splinting the end organ[4]. Though there is no significant curable treatment but there are some internationally proven and well accepted prophylactic medication which reduces headache severity, frequency, duration and risk for rebound[5]. Sodium valproate and pizotifen are commonest of them[6], where sodium valproate is more effective than pizotifen in the prophylaxis of migraine patients.* ***Methods:*** *This study was a single blind randomized clinical trial carried out in the neurology outpatient department of Bangabandhu Sheikh Mujib Medical University, Dhaka (BSMMU) for the period of 2 years, among adult patients between the age of 16-50 years.* ***Results:*** *A total of 120 patients were included & divided into two groups such as group-A(60 patients) treated by sodium valproate & group-B(60 patients) treated by pizotifen for a period of 6 months and followed up every two months for 3 times and showed sodium valproate is more effective than pizotifen.* ***Conclusion:*** *This study permit to conclude that efficacy of sodium valproate is more than pizotifen in the prophylaxis of migraine patients.*

Key words: *migraine ,sodium valproate, pizotifen, prophylaxis.*

Introduction:

Migraine is now ranked by the World Health Organization as number 19 among all diseases causing disability world-wide[1]. The exact cause is unknown but a number of factors trigger a migraine headache e.g. sensory stimuli, streneous exercise & physical exertion, inadequate posture or stress in neck, hormonal fluctuation, foods-drinks & additives, dehydration, insufficient sleep & skipping or missing meal[7]. The exact pathogenesis is still unclear but following possible theories are responsible like vascular theory, neural theory, 5-HT theory, dopamine theory & some other theories[8-10]. It is an episodic primary headache disorder characterized by recurrent attacks of various combinations of headache and neurological, gastrointestinal and autonomic symptoms[2]. Migraine is a common condition, annually affecting

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12% of the United states population, including 18% of women, 6% of men and 4% of children. Lifetime prevalence of migraine in women in the United States exceeds 25%. The prevalence of migraine has not changed since 1989, which was based on evidence from three large studies: American Migraine study-I, American Migraine Study-II and American Migraine Prevention and prevalence study. The basic principle in management of migraine is avoiding the trigger factors, blocking the mediators[4]. Sodium valproate and pizotifen can be used in the prophylaxis of migraine and the potential effectiveness of sodium valproate in migraine prophylaxis is well established.

Materials and Methods:

This study was a single blind randomized clinical trial carried out in the department of neurology at BSMMU, Dhaka from January 2010 to December 2011 for a duration of two years among patients of both sexes between 16-50 years who presented with migraine and were enrolled in this study. Migraine patient were selected according to INTERNATIONAL HEADACHE SOCIETY (IHS) criteria who were not on prophylactic medication & patients having hepatic or renal impairment, pregnancy and prostatism were excluded from the study.

Observation and Results:

A total of 120 patients were included as study population and were divided into two groups, group-A (60 patients) and group-B(60 patients). The group-A took sodium valproate (400-1200 mg/day) and the group-B took pizotifen (0.5-3.00 mg/day) for total 6 months duration.

Table-I

Distribution of the patients by age (n=120)

Age (y)	Group		p value
	Group A (Sodium valproate)	Group B (Pizotifen)	
<20	14 (23.3)#	15 (25.0)	
20 – 29	23 (38.3)	22 (36.7)	
30 – 39	16 (26.7)	17 (28.3)	
40 and above	7 (11.7)	6 (10.0)	
Total	60 (100.0)	60 (100.0)	0.983*

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

Table II

Distribution of the patients by sex (n=120)

Sex	Group A (Sodium valproate)	Group B (Pizotifen)	p value
Male	11(18.3)#	11 (18.3)	1.000
Female	49(81.7)	49 (81.7)	
Total	60 (100.0)	60 (100.0)	

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

Table III

Distribution of the patients by severity before treatment

Severity	Group A (Sodium valproate)	Group B (Pizotifen)	p value
Moderate	21 (35.0)	19 (31.7)	0.699
Severe	39 (65.0)	41 (68.3)	
Total	60 (100.0)	60 (100.0)	

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

Table-I shows in group A majority were in the age group of 20 – 29 years which was 23 (38.3%), followed by 30 – 39 years which was 16 (26.7%) and less than 20 years was 14 (23.3%). Only 7 (11.7%) cases were in the age group of 40 years and above. In group B majority were in the age group of 20 – 29 years, which was 22 (36.7%) followed by group 30 – 39 years which was 17 (28.3%) and less 20 years was 15 (25.0%) cases. Only 6 (10.0%) cases were in the age group of 40 years and above.

Table II shows in both groups females were predominant which was 49(81.7%) and 49(81.7%) cases respectively and statistically significant.

Table III shows in group A moderate was in 21 (35.0%) cases and severe in 39 (65.0%) cases. In group B moderate was in 19 (31.7%) and severe in 41 (68.3%) cases.

Table-IV

Distribution of the patients by duration of episode before treatment (n=120)

Duration of episode	Group		p value
	Group A (Sodium valproate)	Group B (Pizotifen)	
Minutes	1 (1.7)	0 (.0)	0.341
Minutes to hours	40 (66.7)	35 (58.3)	
Hours to days	19 (31.7)	25 (41.7)	
Total	60 (100.0)	60 (100.0)	

*Chi-square test was done to measure the level of significance.

Table-V

Distribution of the patients by frequency of migraine

Group	Frequency of attack			
	Frequency of attack per month before treatment	Frequency of attack per month after 2 months of treatment	Frequency of attack per month after 4 months of treatment	Frequency of attack per month after 6 months of treatment
Group A (Sodium valproate)	7.40 ± 5.1 (3 - 25)	4.69 ± 3.46 (2-20)	2.51 ± 2.20 (1-15)	1.60 ± 1.87 (1 - 10)
Group B (Pizotifen)	9.25 ± 7.21 (2 - 30)	6.56 ± 5.14 (1-20)	3.88 ± 2.83 (1.12)	2.76 ± 1.98 (1 - 8)
p value	0.107	0.022	0.004	0.023

Figure within parentheses indicates percentage.

Table VI

Distribution of the patients by severity after treatment

Severity	Group		p value
	Group A (Sodium valproate)	Group B (Pizotifen)	
Before treatment			0.699
Moderate	21 (35.0)	19 (31.7)	
Severe	39 (65.0)	41 (68.3)	
Total	60 (100.0)	60 (100.0)	
After 2 months of treatment			0.667
Mild	4 (6.7)	2 (3.3)	
Moderate	43 (71.7)	43 (71.7)	
Severe	13 (21.7)	15 (25.0)	
Total	60 (100.0)	60 (100.0)	
After 4 months of treatment			0.234
Mild	44 (77.2)	39 (67.2)	
Moderate	13 (22.8)	19 (32.8)	
Total	57 (100.0)	58 (100.0)	
After 6 months of treatment			0.006
Mild	24 (96.0)	24 (66.7)	
Moderate	1 (4.0)	12 (33.3)	
Total	25 (100.0)	36 (100.0)	

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

Table-VII

Distribution of the patients by duration of episode after treatment (n=120)

Severity	Group		p value
	Group A (Sodium valproate)	Group B (Pizotifen)	
Before treatment			0.341
Minutes	1 (1.7)	0 (0.0)	
Minutes to hours	40 (66.7)	35 (58.3)	
Hours to days	19 (31.7)	25 (41.7)	
Total	60 (100.0)	60 (100.0)	
After 2 months of treatment			0.128
Minutes	26 (44.1)	18 (30.0)	
Minutes to hours	33 (55.9)	40 (66.7)	
Hours to days	0 (0.0)	2 (3.3)	
Total	59 (100.0)	60 (100.0)	
After 4 months of treatment			0.007
Minutes	36 (90.0)	29 (60.4)	
Minutes to hours	4 (10.0)	18 (37.5)	
Hours to days	0 (0.0)	1 (2.1)	
Total	40 (100.0)	48 (100.0)	
After 6 months of treatment			0.010
Minutes	22 (88.0)	20 (51.3)	
Minutes to hours	3 (12.0)	18 (46.2)	
Hours to days	0 (0.0)	1 (2.6)	
Total	25 (100.0)	39 (100.0)	

*Chi-square test wa-s done to measure the level of significance.
#Figure within parentheses indicates percentage.

Table IV shows in group A duration of episode in minutes was in 1 (1.7%) case, minutes to hours in 40 (66.7%) and hours to days in 19 (31.7%). In group B duration of episode in minutes to hours in 35 (58.3%) and hours to days in 25 (41.7%) cases.

Table V shows frequency of attack per month before treatment was 7.40 ±5.1 and 9.25 ± 7.21 in group A and group B respectively (p=0.107). Frequency of attack per month after 2 months treatment was 4.69 ± 3.46 and 6.56 ± 5.14 in group A and group B respectively (p=0.022). Frequency of attack per month after 4 months of treatment was 2.51 ± 2.20 and 3.88 ± 2.83 in group A and group B respectively (p=0.004). Frequency of attack per month after 6 months of treatment was1.60 ± 1.87 and 2.76± 1.98 in group A and group B respectively (p=0.023). and statistically significant.

Table VI shows in group A moderate and severe were 35.0% and 65.0% and in group B moderate and severe were 31.7% and 68.3% respectively (p=0.699). After 2 months of treatment severity was recorded in group A mild, moderate and severe 6.7%, 71.7% and 21.7% cases and in group B mild, moderate and severe 3.3%, 71.7% and 25.0% of cases respectively (p = 0.667). After 4 months of treatment severity was recorded in group A mild and moderate 77.2% and 22.8% of cases respectively and in group B mild and moderate 67.2% and 32.8% of cases respectively (p = 0.234). After 6 months of treatment severity was recorded in group A mild and moderate 96.0% and 4.0% and in group B mild and moderate 66.7% and 33.3% of cases respectively (p = 0.006) and was statistically significant.

Table VII shows, the duration of episode before treatment in group A minutes, minutes to hours and hours to days 1.7%, 66.7% and 31.7% and in group B minutes, minutes to hours and hours to days 0.0%, 58.3% and 41.7% respectively (p=0.341). After 2 months of treatment duration of episode was recorded in group A minutes, minutes to hours and hours to days 44.1%, 55.9% and 0.0% and in group B minutes, minutes to hours and hours to days 30.0%, 66.7% and 3.3% respectively (p=0.128). After 4 months of treatment duration of episode was recorded in group A minutes, minutes to hours and hours to days 90.0%, 10.0% and 0.0% and in group B minutes, minutes to hours and hours to days 60.4%, 37.5% and 2.1% respectively (p=0.007). After 6 months of treatment duration of episode was recorded in group A minutes, minutes to hours and hours to days 88.0%, 12.0% and 0.0% and in group B minutes, minutes to hours and hours to days 51.3%, 46.2% and 2.6% cases respectively (p=0.010) and was statistically significant

Discussion:

In this present study a total of 120 patients were studied and divided into two groups, group-A and group B. The group-A took the sodium valproate and group-B took the pizotifen given with definite doses & duration. In group-A majority were in the age group of 20-29 years which was 23 (38.3%) followed by 30-39 years which was16(26.7%) and less than 20 years which was 14 (23.3%). Only 7 (11.7%) cases were in the age group of 40 years and above. In group-B majority were in the age group of 20 - 29 years which was 22 (36.7%) followed by age group of 30 - 39 years which was 17 (28.3%) and less 20 years which was 15 (25.0%) cases. Only 6 (10.0%) cases were in the age group of 40 years and above. It was reported in a study that migraine usually develops in childhood, adolescence or adulthood[11]. In a study[12] it was also reported that headache intensity declined from 40 years to 74 years with change in headache frequency or duration which is consistent with this study and also consistent with the previous study done in Bangladeshi population[13] .

In both groups female was predominant which was 49(81.7%) cases in group A and 49 (81.7%) cases in group B. Pietrobon D and Striessnig J. reported that female was more vulnerable than male in respect to migraine which is consistent with this present study[11]. Russell et. al.[14] found that there was a significant preponderance of females of all the subtypes of migraine which is also consistent with the present study and also consistent with the previous study done in Bangladeshi populations[13]. The pain severity before treatment revealed that, in group A moderate severity was in 35.0% cases and severe was in 65.0% cases & in

group B moderate was in 31.7% cases and severe was in 68.3% cases (p=0.599). Duration of episode was recorded and it was revealed that in group A minutes was in 1.7% case, minutes to hours was in 66.7% cases and hrs. to days was in 31.7% case. In group B minutes to hours was in 58.3% cases and hours to days was in 41.7% cases. Frequency of attack per month before treatment was 7.40 ±5.1 and 9.25 ± 7.21 in group A and group B respectively (p=0.107). After 2 months of treatment severity was recorded in group A mild, moderate and severe 6.7%, 71.7% and 21.7% cases and in group B mild, moderate and severe 3.3%, 71.7% and 25.0% respectively (p = 0.667). After 4 months of treatment severity was recorded in group A mild and moderate 77.2% and 22.8% cases and in group B mild and moderate 67.2% and 32.8% respectively (p = 0.234). After 6 months of treatment severity was recorded in group A mild and moderate 96.0% and 4.0% cases and in group B mild and moderate 66.7% and 33.3% respectively (p = 0.006). The difference was statistically significant (p=0.009). After 2 months of treatment duration of episode was recorded in group A minutes, minutes to hours and hours to days 44.1%, 55.9% and 0.0% cases and in group B minutes, minutes to hours and hours to days 30.0%, 66.7% and 3.3% cases respectively (p=0.128). After 4 months of treatment duration of episode was recorded in group A minutes, minutes to hours and hours to days 90.0%, 10.0% and 0.0% cases and in group B minutes, minutes to hours and hours to days 60.4%, 37.5% and 2.1% cases respectively (p=0.007). After 6 months of treatment duration of episode was recorded in group A minutes, minutes to hours and hours to days 88.0%, 12.0% and 0.0% cases and in group B minutes, minutes to hours and hours to days 51.3%, 46.2% and 2.6% cases respectively (p=0.010). The difference was statically significant (p=0.01).

Frequency of attack per month after 2 months treatment was 4.69 ± 3.46 and 6.56 ± 5.14 in group A and group B respectively (p=0.022). Frequency of attack per month after 4 months of treatment was 2.51 ± 2.20 and 3.88 ± 2.83 in group A and group B respectively (p=0.004). Frequency of attack per month after 6 months of treatment was 1.60 ± 1.87 and 2.76± 1.98 in group A and group B respectively (p=0.023). The difference is statistically significant (p=0.023) which is consistent with the previous study done in Bangladeshi populations[13]. So, sodium valproate is more beneficial than Pizotifen in the prophylaxis of migraine.

Conclusion:

The finding of this study permit to conclude that the efficacy of sodium valproate is more than Pizotifen in the prophylactic management of migraine patient.

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Comparative Study of Risk Factors Between Lacunar and Non-lacunar Ischemic Strokes

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Abstract:

Background: *Stroke is a leading cause of mortality and morbidity in both developed as well as developing countries The risk factors in lacunar stroke differ in comparison to nonlacunar strokes. In this study risk factors of lacunar stroke in comparison to non-lacunar were evaluated.* ***Objectives:*** *The aim of the study was to compare the risk factors among lacunar stroke and non-lacunar stroke.* ***Methodology:*** *This comparative study conducted in the department of Medicine and Neurology, Dhaka Medical College Hospital, Dhaka from September 2010 to August 2011. MRI of brain was done in 151 patients above 18 years of age with ischemic stroke and Lacunar stroke was found in 31 patients and non-lacunar stroke was detected in 120 patients. Based on the inclusion and exclusion criteria from them 30 patients with lacunar stroke were selected as Group-A patients and equal number of non-lacunar stroke same ages as group B were compared of. The risk factors of stroke were defined as hypertension, diabetes mellitus, hypercholesterolemia, smoking, history of transient ischemic attack, myocardial infarction, atrial fibrillation and carotid artery stenosis.* ***Results****: Out of 151 patients with ischemic stroke non-lacunar stroke was predominant, which was 79.47% and lacunar stroke was 20.52%. The mean age was found 60.9±10.2 years in Group A and 56.2±11.8 years in Group B, which was almost similar between two groups (p>0.05). Male were predominant, which was 63.33% and 76.67% in lacunar and non-lacunar stroke respectively. Male and female ratio was 2.3:1. Regarding the risk factors hypertension was observed most common risk factor among the patients having lacunar and non-lacunar strokes. Hypertension and diabetes mellitus were common in lacunar stroke and myocardial infarction, carotid artery stenosis and hypercholesterolemia were common in non-lacunar stroke which were statistically significant (p<0.05) between the both groups. However, the percentage of smoking, previous TIA and atrial fibrillation were not significantly (p>0.05) different between lacunar and non-lacunar stroke.* ***Conclusion:*** *Hypertension and diabetes mellitus were common in lacunar stroke, and myocardial infarction, whereas carotid artery stenosis and hypercholesterolemia were common in non-lacunar stroke and the both groups were statistically significant (p<0.05) . So modification of risk factors may reduce the incidence of ischemic stroke.*

Key word: *Lacunar stroke, Non-lacunar Strokes, Ischemic stroke*

Abbreviation: *TIA (transient ischemic stroke)*

Introduction:

Stroke is a neurological disease, which is major cause of death and disability worldwide. Stroke kills about five million people each year making this the second major cause of death worldwide. At least fifteen million others have non-fatal stroke annually and about a third are disabled as a consequence[1].The word stroke is used to refer to

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a clinical syndrome of presumed vascular origin, typified by rapidly developing signs of focal or global disturbance of cerebral functions lasting more than 24 hours or leading to death[2].It is the outward manifestation of a localized sudden interruption of the blood supply to some parts of the brain on etiological basis, of all strokes about 85% are ischemic and 15% are hemorrhagic[3]. In a hospital based study in Bangladesh among stroke patients, it was found that 57.84% were ischemic and 42.16% were haemorrhagic[4]. Ischemic stroke occurs either due to thrombosis or embolism involving the cerebral circulation and categorized as small vessel lesion and large vessel lesion[5]. This distinction can usually be made by means of clinical features and more reliably by CT or MRI scanning[6].Around 70% of the thrombotic strokes are due to large artery thrombosis and remaining are small infarcts or lacunars infarcts [7].

Lacunar stroke has been regarded as the least severe subtype of ischemic stroke for many years[8].Symptomatic lacunar stroke was defined as a stroke presenting one of the 5 classic lacunar syndromes (pure motor stroke ,pure sensory stroke, sensorymotor stroke, ataxic hemiparesis, and dysarthria – clumsy hand syndrome) and confirmed by small (<15mm in diameter) subcortical infarct on brain MRI in the absence of any other morphological cause of ischemic stroke found on the neuroimaging examination[9].These are presumed to result from the occlusion of single, small, perforating arteries supplying the deep subcortical areas of the brain. If the occlusive arterial pathology is distinct from the atherothromboembolic processes that occlude larger arteries, causing most other types of ischemic stroke, the best strategies for the investigation and treatment of patients with lacunar infarction might differ from those for patients with other ischemic stroke subtypes. The arterial pathology of lacunar infarction is based largely on Fisher's meticulous clinicopathological studies, in which he serially dissected the vascular supply of a total of 68 lacunar infarcts in 18 postmortem brains[10]. To be defined as a lacunar stroke by MRI, the following criteria had to be met: (1) be round or oval in shape; (2) measure <1.5 cm in diameter; (3) be located in the typical territory supplied by deep or superficial small perforating arteries; (4) not be in cortical territories; and (5) not have the morphological and topographical distribution consistent with partial internal border-zone infarcts[11].

Non-lacunar ischemic stroke was defined as either e"2 of the following symptoms: (1) higher cerebral dysfunction (e.g., dysphasia, dyscalculia, visuospatial disorder); (2) homonymous visual field defect; and (3) ipsilateral motor or sensory deficit, or higher cerebral dysfunction alone or a motor or sensory deficit more restricted than those classified as lacunar (e.g., confined to one limb, face, or hand but not the complete arm) and additionally MRI of brain following the event had to show an appropriate cortical, subcortical or combined lesion of > 1.5 cm diameter in the absence of an obvious cardioembolic source[12].

Pathological studies are rare because autopsy rates are declining, lacunar strokes have a low-case fatality rate[8] and tracing the vascular supply of subcortical lesions is technically difficult and time consuming[10].Difficulties in imaging the small perforating intracranial arteries has made informative imaging studies scarce. An alternative approach has been to compare the risk factor profiles of patients with lacunar infarcts versus those with non-lacunar infarcts because this may reveal differences suggestive of distinct arterial pathologies.

The cause of lacunar infarction is occlusion of a single small penetrating artery. This occlusion may be due to microatheroma and lipohyalinosis, which are associated with hypertension, smoking, and diabetes, or may result from microembolism from the heart or carotid arteries [7,12].Atrial fibrillation and ipsilateral carotid stenosis have a stronger association with non-lacunar infarcts[13].

Materials and Methods:

This Observational comparative study was conducted in the department of Medicine and Neurology, Dhaka Medical College Hospital, Dhaka from September 2010 to August 2011. MRI of brain was done in 151 patients above 18 of age years with ischemic stroke and lacunar stroke was found in 31 patients and non-lacunar stroke was detected in 120 patients.

Inclusion criteria: were 1) Evidence of lacunar/ non-lacunar infarct by MRI of brain 2) History of first ever ischemic stroke.3) Presenting within two weeks of symptoms. 4) Adult patients Age: 18 years and above Exclusion criteria: 1) MRI of brain not showing a relevant lesion. 2) History of recurrent stroke. 3) Not willing to be included in the study. 4) Age less than 18 years.

MRI of brain was done to every patient to confirm the diagnosis lacunar and non-lacunar stroke by 'AIRIS ²I Hitachi' MRI machine (0.3 Tesla). MRI of brain of all patients was reviewed by the same consultant radiologist in DMCH blinded to the clinical data and to any hypothesis about this study. Following the above inclusion and exclusion criteria from them 30 patients with lacunar stroke were selected as Group-A patients and equal number of non-lacunar stroke same ages as group B were compared The risk factors of stroke were defined as hypertension; diabetes mellitus ; hypercholesterolemia ; smoking ; history of transient ischemic attack; myocardial infarction; atrial fibrillation and carotid stenosis Data was collected by face-to-face interview, physical examination and investigations in a data collection sheet.. On admission detailed history and thorough clinical examination including neurological assessment was carried out. Emphasis was given on risk factors especially hypertension and diabetes mellitus. Patients who presented with sudden onset of lateralizing signs especially in the presence of atrial fibrillation, rheumatic heart disease, recent myocardial infarction and carotid bruit were considered to be suffering from ischemic stroke. In addition to routine investigation fasting blood sugar, lipid profile, ECG and in some selected patient echocardiography and Duplex Ultrasound of carotid (extracranial) vessels were done . Study was intended to evaluate risk factors and clinical presentation in lacunar and non-lacunar strokes.

Statistical analyses related with this study were performed by use of SPSS 12 package program The comparisons between patients with lacunar and non-lacunar stroke with the Student t test for normally distributed continuous variables and $\div^2$ tests for dichotomous variables. Test of performance were done to detect the sensitivity, specificity, positive predictive value, negative predictive value and accuracy. Ethical clearance is taken from ethical committee of DMCH. Every patient and/or responsible family member will be asked for informed consent about the procedure and the study goal.

Observation and Results:

Table-I

Frequency of patients with lacunar and non-lacunar stroke

No of patients with Ischemic stroke	Group A Lacunar stroke	Group B Non-lacunar stroke
151	31(20.52%)	120(79.47%)

Table I shows, a total of 151 patients with ischemic stroke were included in this study. In Group A, 31(20.52%) patients were lacunar stroke and 120(79.47%) patients were non-lacunar stroke. In this study the incidence of non-lacunar strokes were more common than lacunar strokes.

Table-II

Age distribution of the study patients (n=60)

Age (in years)	Group A (n=30)		Group B (n=30)		P Value
	N	%	N	%	
<40	0	0.0	1	3.3	
41-50	3	10	7	23.3	
51-60	7	23.3	11	36.66	
61-70	13	43.33	8	26.66	
71-80	9	30	3	10	
>80	1	3.3			
Mean ±SD	60.9±10.2		56.2 ±11.8		0.104^{ns}
Range (min-max)	(41-85)		(38 – 80)		

ns=Not significant, P value reached from unpaired t-test.

A total of 60 patients were included in the study. They were divided into six groups according to age (Table II). Majority of the patients was found in the age group of 61-70 years in group A, which was 13(43.33%) and 51-60 years in group B, which was 11(36.66%). The mean age was found 60.9±10.2 years in Group A and 56.2±11.8 years in Group B. The mean age difference was not statistically significant (p>0.05) between the patients with lacunar stroke and non-lacunar stroke in unpaired t-test.

Table-III

Sex distribution of the study patients (n=60)

Sex	Group A (n=30)		Group B (n=30)		P Value
	N	%	N	%	
Male	19	63.33	23	76.67	0.259^{ns}
Female	11	36.67	7	23.33	

ns= Not significant ,P value reached from chi square test.

Table-IV

Distribution of the respondents according to risk factors (n=60)

Risk Factors	Group A (n=30) Lacunar stroke		Group B (n=30) Non-lacunar stroke		P Value
	N	%	N	%	
Hypertension	27	90.0	19	63.3	0.014^{s}
Smoking	11	36.67	17	56.66	0.120^{ns}
Diabetes mellitus	17	56.70	9	30.00	0.037^{s}
Myocardial Infarction	5	16.70	13	43.30	0.024^{s}
Carotid artery stenosis(>50%)	7	23.30	17	56.70	0.008^{s}
Hypercholesterolemia	9	30.00	17	56.70	0.037^{s}
Previous TIA	5	16.66	7	23.33	0.518^{ns}
Atrial fibrillation	2	6.66	5	16.66	0.211^{ns}

*Multiple responses . s=Significant, ns=Not Significant ,P value reached from chi square.

Table III shows, in Group A, 19(63.33%) patients were male and 11(36.67%) patients were female. In Group B, 23(76.67%) patients were male and 7(23.33%) patients were female. Not significant (p>0.05) difference was found between patients with lacunar and non-lacunar stroke regarding sex distribution. Male female ratio was 2.3:1 in the whole study patients.

Regarding the risk factors hypertension was observed most common risk factor in the study patients having lacunar and non-lacunar strokes (Table IV). Hypertension and diabetes mellitus were common in lacunar stroke, and myocardial infarction, carotid artery stenosis and hypercholesterolemia were common in non-lacunar stroke which were statistically significant (p<0.05) in chi square test. However, the percentage of smoking, previous TIA and atrial fibrillation were not significantly (p>0.05) different between lacunar and non-lacunar stroke.

Discussion:

This observational comparative study was carried out with an aim to compare risk factors (i.e. Hypertension, diabetes mellitus, smoking; dyslipidemia, previous transient ischemic attack, myocardial infarction and carotid stenosis) between lacunar and non-lacunar strokes as well as their partial demographic profile. The study was carried out in patients attending in inpatient and outpatient Department of Neurology and Department of Medicine in DMCH from September 2010 to August 2011. A total of 200 patients clinically diagnosed as stroke were selected. Detailed history, physical examination and CT scan of Head in every patient

was done by the investigator and findings were recorded. Out of them 151 patients were ischemic stroke and 49 patients were hemorrhagic stroke. MRI of brain was done in all patients with ischemic stroke. Lacunar stroke was found in 31 patients and nonlacunar stroke was detected in 120 patients. Based on the inclusion and exclusion criteria 30 patients with lacunar stroke were selected as Group-A from 31 patients and another 30 patients with age and sex matched patients having non-lacunar stroke were selected from 120 patients as Group-B .

In this current study (Table I), it was observed that out of 151 patients with ischemic stroke non-lacunar stroke was predominant than lacunar stroke, which was 79.47% in and 20.52% in respectively. Similarly, Kaul et al. (2000)[14] undertaken a study on 893 patients of ischaemic stroke in the stroke registry of Nizam's institute of Medical Sciences, Hyderabad and majority of patients with ischemic stroke were non-lacunar stroke (84%) and sixteen percent (16%) of them had lacunar infarction.

Cupini et al. (2002)[11] observed that of 292 adult patients with an acute first-ever ischemic stroke, 96(32.87%) were considered lacunar and 196(67.12%) were considered non-lacunar strokes in their study. The above findings strongly support the current study.

Khan et al (2009)[15] found the mean age of patients with ischemic stroke was 60.34 ±13.24 years ranging from 21- 103 years. Majority of patients (33%) were in the age of 7th decade, followed by patients in 6th decade[14], which closely resembled with the current study, where the current study (Table II) found the mean age was 60.9±10.2 years in Group A and 56.2±11.8 years in Group B, which was almost similar between two groups (p>0.05). Singh et al. (2006)[16] observed in their study that the mean age of the patients was 58.6±12 years ranging from 25 to 85 years which closely resembled with the current study. On the other hand, Homurg et al. (2010)[17] has observed higher mean age in their study patients which were 64±13 years and 61±13 years in Group A and in Group B respectively,the higher age range may be due to increased life expectancy in their study patients.

In this current study (Table III) it was observed that male was predominant, which were 63.33% and 76.67% in group A and group B respectively. Male female ratio was 2.3:1 in the whole study which was slightly higher than those reported from elsewhere. May be this is a reflection of low tendency of female patients for seeking medical advice in tertiary hospital rather relying on treatment of rural doctors as in other parts of the developing world . Bejot et al. (2008)[13] reported that the incidence of lacunar infarcts was significantly higher in men than in women. Similarly, Mohammad et al. (2003)[18] observed that males were predominately affected than females from stroke. Ali et al. (1998)[19] found in their study that most of the stroke patients were male, and male female ratio was 2:1. All these observations closely resemble with the current study where male and female ratio was 2.3:1 and 3.2:1 in lacunar stroke and non-lacunar stroke respectively. The above findings strongly support the current study.

In this series (Table IV) it was observed that smoker was found in 36.67% patients with lacunar stroke and in 56.66% in nonlacunar stroke, which was not significantly (p>0.05) higher in patients having lacunar strokes. Cupini et al. (2002)[11] showed smoking among 35.4% and 33.2% of patients with lacunar and non-lacunar stroke respectively which was not significant (p>0.05), but was consistent with the current study. Similarly, Tejada et al. (2003)[20] showed smokers were almost similar between two groups.

In this current series it was observed that 90% and 63.33% patients were hypertensive in patients with lacunar and non-lacunar stroke respectively, which was significantly (p<0.05) higher in patients having lacunar strokes. Similarly, Khan et al. (2007)[21] have showed hypertension 88.6% in group A and 71.2% group B. Jackson and Sudlow (2005)[22] identified hypertension as a significant risk factor for lacunar stroke compared with non-lacunar ischemic stroke. Jackson and Sudlow et al. (2005)[22] mentioned in their study that the apparent excess of hypertension in lacunar infarction was confined to studies in which the presence of hypertension favored a diagnosis of lacunar infarction (pooled RR, 1.25; 95% CI, 1.21 to 1.28).

In this study it was observed that diabetes mellitus was significantly ($p<0.05$) higher in patients having lacunar strokes, which was 56.7% in group A and 30.0% in group. B. Kaul et al. (2000)[14] reported that patients with lacunar infarction had higher frequency of diabetes and absence of significant (>50%) extracranial carotid artery disease. Similarly, Jackson and Sudlow et al. (2005)[22] mentioned that there was a significant excess of diabetes in lacunar versus nonlacunar infarction among studies using a classification in which diabetes favors a diagnosis of lacunar infarction (pooled RR, 1.25; 95% CI, 1.17 to 1.34). Jackson and Sudlow (2005)[22] suggested that the current trend of using the TOAST classification system could overestimate the role of hypertension and diabetes in lacunar stroke, as the criteria stipulate that a history of hypertension and diabetes may be useful indicators to the existence of SVD. All the above findings are consistent with the current study.

The atrial fibrillation of the present study patients was found 6.66% in group A and 16.66% in group B. In this study the incidence of atrial fibrillation was more in non-lacunar stroke than lacunar stroke that was not statistically significant ($p>0.05$). The frequency of atrial fibrillation was found to be higher in non-lacunar in some studies .Cupini et al. (2002)[11] showed atrial fibrillation was 4.2% in lacunar stroke and 23.5% in non-lacunar stroke. In another study Jackson and Sadlow et al. (2005)[22] demonstrated the association of AF with non-lacunar infarction was particularly pronounced among studies in which the presence of atrial fibrillation favored a diagnosis of non-lacunar infarction, which support the current study findings.

In this present series it was observed that myocardial infarction was found 16.7% patients having lacunar stroke and 43.3%patients having non-lacunar stroke, that was significantly ($p<0.05$) higher in patients having non-lacunar strokes. Similarly, Baumgartner et al. (2003)[23] myocardial infarction was 5.3% and 18.0% in lacunar and non-lacunar stroke respectively ($p<0.05$), which is consistent with the current study. In Khan et al. 2007 study myocardial infarction was significantly higher in patients with non-lacunar stroke[27].

In this present series it was observed that carotid stenosis, was significantly ($p<0.05$) higher in patients having nonlacunar strokes than patients having lacunar stroke, which was 23.3% in group A and 56.7% in group B. Similarly, Cupini et al. (2002)[11] have showed 16.7% and 24.5% patients had carotid stenosis in lacunar and nonlacunar stroke respectively. Several studies showed overall, there was an excess of ipsilateral carotid stenosis among patients with non-lacunar infarction[24-27]. The association was more pronounced in Jackson and Sudlow (2005)[22] study in which severe carotid stenosis favored a diagnosis of non-lacunar infarction and similar result was observed for contralateral stenosis. The above findings are comparable with the current study.

Previous TIA was found in 6.66% among group A and 16.66% among group B patients in this study. There was some difference of incidence of previous TIA between lacunar and non-lacunar strokes in this series, which was not significantly ($p>0.05$) higher in patients of both groups. In another study done by Cupini et al. (2002) [11] did not find a significantly different percentage of previous TIA between the 2 groups of patients having lacunar and non-lacunar stroke.

Conclusion:

To compare risk factors (i.e. Hypertension, diabetes mellitus, smoking, hypercholesterolemia, previous transient ischemic attack, myocardial infarction and carotid stenosis) between lacunar and non-lacunar strokes majority of the patients was found in 7th and 6th decade in lacunar and non-lacunar strokes respectively and male was predominant. Smoking status was almost similar between two groups. Hypertension and diabetes mellitus were significantly ($p<0.05$) higher in patients having lacunar strokes however, carotid stenosis, myocardial infarction, hypercholesterolemia were significantly ($p<0.05$) higher in patients having non-lacunar strokes. However, the percentage of smoking, previous TIA and atrial fibrillation were not significantly ($p>.05$) different between lacunar and non-lacunar stroke.

Study limitation:

This study was based on data collected from Neurology ward and Medicine ward of a tertiary level hospital. As this study was based on a tertiary

level hospital so, the sample size was small, the findings may not represent overall population of our country. Majority of the stroke patients were not referred to such a tertiary care hospital and only the more severe cases were admitted. Further community based large sample studies are required to have an unbiased observation.

Recommendation:

Ischemic stroke management depends on stroke subtype. Cardio-embolic and artery to artery embolus are very uncommon cause of lacunar stroke and study suggests that patients with lacunar stroke may not require detailed evaluation of carotid artery or cardio-embolic sources. This study also strongly recommends that along with subtyping, determination of risk factors is essential for etiopathological correlation, management plan and outcome prediction both in lacunar and non-lacunar stroke. Risk factors should be studied to ensure better stroke care.

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Bangladesh Journal of Neuroscience 2012; Vol. 28 (2) : 96-101

Comparison of Clinical Diagnosis of Stroke with Computed Tomographic Scan of the Brain

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Abstract:

Background and purpose*: Stroke is a leading cause of mortality and morbidity in both developed as well as developing countries. The clinical presentation of stroke depending on the site and extent of lesions. For the management purpose it is important to know whether we are dealing with a bleed or an infarct* ***. Methodology:*** *Computed Tomography (CT scan) is available most of the tertiary level hospitals in Bangladesh. This study was carried out to compare clinical diagnosis of stroke with Computed tomography (CT) scan findings in ascertaining the type of stroke (hemorrhagic or ischemic). Materials and methods: This cross-sectional comparative study was conducted in the Department of Neurology, Rajshahi Medical College Hospital during the period of January 2010 to December 2010. Total 200 stroke patients were selected by purposive sampling technique on the basis of inclusion and exclusion criteria as the study sample. . CT brain scan was done for all the patients. The clinical diagnosis was compared with the results of CT scan and performance test was done.* ***Results****: Clinically 67 patients were diagnosed as hemorrhagic stroke and 133 patients were diagnosed as ischemic stroke. Out of these 67 hemorrhagic patients CT scan revealed that 56 patients had intracerebral hemorrhage, 5 had infarct, 4 had subarachnoid hemorrhage and 2 had space occupying lesions in the brain. Out of these 133 ischemic patients CT scan revealed that 119 patients had infarction, 6 had intracerebral hemorrhage and 8 had space occupying lesions in the brain. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of clinical diagnosis of hemorrhagic stroke were 90.32%, 92.03%, 83.58%, 92.02% and 91.5% respectively. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of clinical diagnosis of ischemic stroke were 95.96%, 81.58%, 89.47%, 92.53% and 90.5% respectively.* ***Conclusion:*** *The diagnosis of stroke in clinically with high accuracy, but perform a CT scan will help to confirm and differentiate to type stroke. Thus CT scan should be done in all cases stroke to specify the diagnosis.*

Key Words: *Stroke, Computed Tomography Scan.*

Introduction:

Cerebrovascular diseases include some of the most common and devastating disorders: ischemic stroke, hemorrhagic stroke, and cerebrovascular anomalies such as intracranial aneurysms and arterio-venous malformations. They cause 200,000 deaths each year in the United States and are a major cause of disability. The incidence of cerebrovascular diseases increases with age, and the number of strokes is projected to increase as the elderly population grows, with a doubling in stroke deaths in the United States by 2030[1]. Stroke

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is a one of the leading cause of mortality and morbidity in both developed as well as developing countries like Bangladesh. The clinical picture and epidemiology is variable depending on the site and extent of lesions [2].

Stroke is defined by this abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Thus, the definition of stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature[1].

The differentiation of cerebral infarction and cerebral haemorrhage is the most important first step in the management of acute stroke, because clinical management of the two disorders differs substantially [3]. The distinction between cerebral infarction (CI) and intracerebral haemorrhage (ICH) is now seen as crucial in determining prognosis and acute care and to promote secondary stroke prevention. Certain drugs or procedures may benefit patients with CI but they are potentially dangerous in those with haemorrhage. The classic clinical features of ICH (sudden onset with severe headache, vomiting, rapid deterioration of consciousness, lack of previous transient events) are frequent and reasonably specific only in massive haemorrhage. However, distinction between CI and small or superficial haemorrhages using these simple criteria seems to be considerably more difficult. To deal with this problem, clinical scoring systems including several variables have been constructed and are considered to be more accurate than unstructured clinical diagnosis as usually made in clinical practice. Instruments commonly used for this purpose include those from the Guys Hospital, from Siriraj Hospital and from the Grenoble University Center [4].

The introduction of computed tomography (CT) to clinical practice has had a great impact on our knowledge of cerebrovascular disorders, and cerebral CT has become the most commonly used primary radiologic investigation for stroke. Cerebral CT has shown that the prognosis of intracerebral hemorrhage (ICH) is not as poor as was supposed when small hemorrhages were often undiagnosed or misdiagnosed as ischemic events, and it has changed the order of diagnostic procedures for stroke. Furthermore, in differentiating ischemic infarcts from hemorrhagic lesions, cerebral CT has proved to be of crucial importance for therapeutic considerations, particularly anticoagulant treatment [5].

The radiologic diagnosis of stroke requires accurate detection and appropriate interpretation of relevant imaging findings; both detection and interpretation may be influenced by knowledge of the patient's presentation. Availability of a clinical history indicating that early stroke is suspected significantly improves the sensitivity for detecting strokes on non-contrast CT without reducing specificity. Whenever possible, relevant clinical history should be made available to physicians interpreting emergency CT scans of the head[6]. Even then treatment for acute ischemic stroke is now being carried out before brain images have become positive, increasing reliance is being placed on early clinical assessment [7]. For faster access to acute stroke treatments, quicker transfer to stroke units and earlier secondary stroke prevention, stroke and TIA patients need to be accurately identified in the emergency department [8].

Materials and Methods:

This cross-sectional comparative study was conducted in the Department of Neurology, Rajshahi Medical College Hospital (RMCH) during the period of January 2010 to December 2010. *Two Hundred suspected acute stroke patients were selected* by purposive sampling technique with inclusion criteria were, 1)Patient presenting with acute onset focal neurological deficits , 2)Neurological deficit lasting for more than 24 hours and 3)Age: 18 years or above and exclusion criteria were 1) Recurrent stroke. 2) Stroke duration of more than 14 days because of the possibility of missing an intracerebral haemorrhage. 3) Stroke associated with hematological conditions like leukemia, polycythaemia and 4) Metabolic disorders like hypoglycemia.

Data will be collected by face-to-face interview, physical examination and investigations in a data collection sheet.. On admission detailed history and thorough clinical examination including neurological assessment were carried out. Emphasis was given on risk factors especially hypertension, coronary artery disease, atrial fibrillation, rheumatic heart disease, peripheral vascular disease, smoking and diabetes mellitus etc. The clinical diagnosis of type

of stroke was made on the basis of the neurological history and signs. Those patients who presented with sudden onset of coma, rapid deterioration of neurological state, severe headache and vomiting and neck stiffness along with hypertension were considered to be suffering from hemorrhagic stroke. Patients who presented with sudden onset of lateralizing signs especially in the presence of atrial fibrillation, rheumatic heart disease, recent myocardial infarction and carotid bruit were considered to be suffering from ischemic stroke. In addition to routine investigation s, blood sugar, lipid profile, ECG and in some selected echocardiography were performed. All patients had CT scan brain were done in all patients from the department of radiology . Then the clinical diagnosis was compared with the results of CT scan and precision of clinical diagnosis was ascertained.

Statistical analyses related with this study were performed by using of SPSS 13 package program The comparisons between patients with hemorrhagic and ischemic stroke with the student t test for normally distributed continuous variables and χ^2 tests for dichotomous variables. Test of performance were done to detect the sensitivity, specificity, positive predictive value, negative predictive value and accuracy. Ethical clearance is taken from ethical committee of RMCH. Every patient and/or responsible family member will were asked for informed consent about the procedure and the study goal.

Results and Observation:

Table-I

Demographic status of the patients

	Hemorrhagic (n=67)	Infarction (n=133)	p value
Age of the patients (Mean±SD)	57.61±8.3	56.30±9.70	.346^{NS}
Sex of the patients, frequency (%)			
Male	35(52.2%)	63(47.4%)	.515 ^{NS}
Female	32(47.8%)	70(52.6%)	

The p value of categorical variables were obtained by chi-square test and continuous variables by Student't' test.

The Table-I shows, the mean (±SD) age of the patients with hemorrhagic stroke was 57.61(±8.3) years and the mean (±SD) age of the patients with ischemic stroke was 56.3(±9.7) years. The difference of mean age between two groups were not statistically significant (p>0.05).Among the patients with hemorrhagic stroke 35(52.2%) were male and 32(47.8%) were female. Among the patients with ischemic stroke 63(47.4%) were male and 70(52.6%) were female. The difference of gender between two groups were not statistically significant (p>0.05).

Table-II

Clinical diagnosis of type of stroke

Clinical diagnosis of type of stroke	Frequency	Percent
Hemorrhagic	67	33.5
Ischemic	133	66.5

Table III

Cross tabulation of clinical type of stroke and diagnosis by CT scan

		Clinically diagnosed type of stroke		Total
		Hemorrhagic	Infarction	
Diagnosis by CT Scan of Brain	Hemorrhage	56 (83.6%)	6 (4.5%)	62 (31.0%)
	Infarction	5 (7.5%)	119 (89.5%)	124 (62.0%)
	SAH	4 (6.0%)	0 (0.0)	4 (2.0%)
	SOL	2 (3.0%)	8 (6.0%)	10 (5.0%)
	Total	67 (100%)	133 (100%)	200

Table-IV

Performance of clinical diagnosis in diagnosing hemorrhagic stroke

Diagnostic Modality		Diagnosis by CT Scan		Total
		Hemorrhagic	Other than hemorrhage	
Clinical type of Stroke	Hemorrhage	a = 56	b = 11	a+b = 67
	Other than hemorrhage	c = 6	d = 127	c+d = 133
	Total	a + c = 62	b + d = 138	N=b+c+d =200

Table II, shows that among the 200 patients 67(33.5%) patients were diagnosed as hemorrhagic stroke and 133(66.5%) patients were diagnosed as infarctive stroke

From table III, it was revealed that, clinically 67 patients were diagnosed as hemorrhagic stroke. Out of these 67 patients CT scan revealed that 56 (83.6%) patients had intracerebral hemorrhage, 5 had infarct, 4 had subarachnoid hemorrhage and 2 had space occupying lesions in the brain. Clinically 133 patients were diagnosed as having infarction. Out of these 133 patients, CT scan revealed that 119 patients had infarction, 6 had intracerebral hemorrhage and 8 had space occupying lesions in the brain.

The Table IV shows that the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of clinical diagnosis of hemorrhagic stroke were 90.32%, 92.03%, 83.58%, 92.02% and 91.5% respectively.

Discussion:

The present study (Table I) revealed that the mean (±SD) age of the patients with hemorrhagic stroke was 57.61(±8.3) years and the mean (±SD) age of the patients with ischemic stroke was 56.3(±9.7) years. Among the patients with hemorrhagic stroke 35(52.2%) were male and 32(47.8%) were female. Among the patients with ischemic stroke 63(47.4%) were male and 70(52.6%) were female. The findings of the present study were supported by Baloch et al (2009), studied in the Liaquat University Hospital, Hydrabad, India[9]. Among a total of 110 patients Baloch et al (2009) found that 60 (54.5%) were males and 50 (45.5%) were females. Age of patients ranged 22-84 years with mean (±SD) age of 53(±5) years. In the present study (Table II) among the 200 patients 67(33.5%) patients were clinically diagnosed as hemorrhagic stroke and 133(66.5%) patients were diagnosed as ischemic stroke. Out of 67 clinically diagnosed hemorrhagic stroke patients CT scan revealed that 56 patients had intracerebral hemorrhage, 5 had infarct, 4 had subarachnoid hemorrhage and 2 had space occupying lesions in the brain. Out of 133 clinically diagnosed ischemic stroke patients CT scan revealed that 119 patients had infarction, 6 had intracerebral hemorrhage and 8 had space occupying lesions in the brain.

Among a total of 110 patients Baloch et al (2009) found that on clinical ground cerebral infarction was suspected in 89 (80.9%) and cerebral hemorrhage in 21 (19.1%) patients[9].Based on clinical features, 62% of patients were categorized as cerebral infarcts and 30% and 8% were diagnosed as intracerebral and subarachnoid hemorrhage, respectively. CT scanning revealed that 8% of patients with clinical diagnosis of stroke were having other cerebral pathology (4% hydrocephalus, 4% cerebral tumor) [10].

Khan and Rahman (2005) found that CT scan brain showed 60% cerebral infarction, 27% intracerebral hemorrhages, 9% space occupying lesion and 4% hemorrhagic infarct[11].Siddique et al (2009) conducted a study among 100 stroke patients in Chittagong Medical college hospital of Bangladesh. Ischemic stroke was found in 80% cases and hemorrhagic stroke was found in 20% cases [12]. Whiteley et al (2011)o conducted a cross-sectional study among 405 patients with suspected stroke, of whom 285 (70%) had symptoms owing to a final diagnosis of probable or definite acute cerebrovascular diseases, and 120 (30%) owing to other illness[8].

Hill (2010) stated that ischaemic stroke is the most common stroke type, comprising 65-85% of all stroke, varying by location in the world. Two main haemorrhagic forms of stroke are intracerebral hemorrhage (ICH) and subarachnoid haemorrhage[13].

Wardlaw (1994) observed that outside hospital about 80% of strokes are cerebral infarcts, 10% are primary intracerebral haemorrhages, 5% are subarachnoid haemorrhages, and about 5% are of uncertain cause. Wardlaw (1994) also observed that in hospital only 60-75% of patients with stroke have a cerebral infarct [14].

Naik et al (2006) stated that there are four major types of stroke, eg: cerebral infarction, intracerebral haemorrhage (ICH), primary subarachnoid hemorrhage (SAH) and venous occlusion. Cerebral infarction is due to significantly diminished blood flow to all parts of the cerebral

hemisphere (global) or selected areas (regional or focal) of the brain. Naik et al (2006) found that among the stroke subtypes, cerebral ischernia and infarction constitute about 85-90% of the total stroke subtypes in western countries with only about 10-15% patients with cerebral haemorrhage. But contrary to the western population, hemorrhagic stroke constitutes a larger percentage of stroke subtypes on this side of the globe as seen in countries like Japan and China probably because of poorly controlled hypertension[15].

Sotaniemi, Pyhtinen, Myllyla (1990) studied 1,191 consecutive patients with acute cerebrovascular disease and found that computed tomography scan revealed hemorrhagic lesion in 33.8%, ischemic in 66.2% and a significant non-stroke abnormality in 3.1%. They emphasized that both careful neurologic assessment and a policy of early computed tomography scan are of crucial importance in the diagnosis of stroke and for therapeutic consideration[5].

In the current study (Table III), the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of clinical diagnosis of hemorrhagic stroke were 90.32%, 92.03%, 83.58%, 92.02% and 91.5% respectively. In case of ischemic

stroke (Table IV) the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 95.96%, 81.58%, 89.47%, 92.53% and 90.5% respectively.

To develop a simple, reliable, and safe diagnostic tool for acute stroke syndromes in a setting where computerized brain scanning was not readily available, The Siriraj Stroke Scale was developed in Mahidol University, Bangkok [16] and was calculated a score above 1 indicates supratentorial intracerebral haemorrhage, while a score below -1 indicates infarction. The score between 1 and -1 represents an equivocal result needing a computerized brain scan or probability curve to verify the diagnosis. In the validation study of the Siriraj stroke score the diagnostic sensitivities of the score for cerebral haemorrhage and cerebral infarction were 89.3% and 93.2% respectively, with an overall predictive accuracy of 90.3%.[17,18] To improve the clinical diagnosis of stroke in the emergency department, Nor, et al[2 19] formulated the ROSIER scale (Recognition of Stroke in the Emergency Department). Rapid assessment and triage by paramedics had achieved a consistent diagnostic accuracy of between 80% and 95% and so, this study is consistent with our study[19].

Conclusion:

The diagnosis of strokes can be done clinically with high accuracy, but a CT scan of brain will help to confirm the diagnosis and differentiate the types stroke. Thus CT scan should be done in all of cases strokes to confirm the diagnosis.

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Bangladesh Journal of Neuroscience 2012; Vol. 28 (2) : 102-107

Posterior Decompression with Fusion & Fixation by Pedicle Screw and Rod of Thoraco Lumbar Spine: A Study of 15 Cases

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Abstract:

Background & Objectives: *Thoraco-lumbar fracture is one of the common problems in spinal injury patients. It's early management can prevent complication after injury and can improve neurological function. The treatment plan of unstable fracture is controversial.* ***Methods:*** *The study was carried out at the department of neurosurgery, Bangabandhu Sheikh Mujib Medical University from June 2010 to July 2011 among the patients admitted with thoraco-lumbar spine fracture.* ***Results:*** *A total number of 15 patients with thoraco-lumbar spine fracture were included in the study. Among the 15 patients, 13(86.66%) were male. The highest number of patients were in age group of 1-20(40%) and 21-40(40%) years. The commonest cause of Thoraco-lumbar spine injuries were fall from height which was 8(53.33%) in number. The commonest site of injury was L_1 fracture in 4(60%) patients. It was documented that bladder dysfunction and lower limb weakness were the commonest sign. It was evident that, 10(66.70%) and 4(26.66%) of the patients were partially and completely improved after surgery respectively and 3(10%) of patients had wound infection.* ***Conclusion:*** *Thoraco-lumbar spine fracture with incomplete injury, early surgery can improve many of the patient's life.*

Key word: *Thoraco-lumbar, fracture, posterior decompression, fusion, fixation, pedicle screw.*

Introduction:

About 64% of spine fractures occur at the thoraco-lumbar (TL) spine , usually at T12-L1 level and 70% of these occur without immediate neurologic injury. Denis 3 column model of the spine attempts to identify CT criteria of instability of thoraco-lumbar spine fractures[1].This model has generally good predictive value, however, any attempt to create "rules" of instability will have some inherit inaccuracy[1].

The McAfee classification describes 6 main types of fractures[2]. A simplified system with four categories follows. Lateral and anterior most common between T6-T8 and T12-L3. Lateral X-ray wedging of the vertebral body(VB) anteriorly, no loss of height of posterior VB, no subluxation. CT spinal canal intact. Disruption of the anterior end plate[2].

The thoraco-lumbar injuries are the commonest spinal injuries[3]. The treatment of unstable fractures and fracture dislocations of thoraco-lumbar spine remains controversial[4]. The goal of the treatment of unstable thoraco-lumbar injuries is optimizing neural decompression while providing stable internal fixation over the least number of spinal segments[5]. Either anterior posterior or both approaches can be used to achieve fusion[6]. However, posterior approach is less extensive. Pedicle screw devices allow immediate stable fixation as the screws traverse all the three columns. The pedicle screws are passed one level above and one level below the fractured vertebra via posterior approach[7].

Injuries to the thoracic and lumbar spine account for > 50% of all spinal fractures and a large portion of acute spinal cord injuries[8]. Given this frequency and the significant impact of these injuries,

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significant advancements have been made in the surgical treatment of thoraco-lumbar trauma. Despite the invention and continued evolution of spinal instrumentation and surgical techniques, medical decision-making in spine trauma remains controversial. Fracture treatment can vary widely, from bracing to invasive 360° fusions, based on geographical, institutional, or individual preferences with little scientific basis[8].

A number of classification systems have been developed in an attempt to better define thoraco-lumbar trauma and aid treatment decision-making. These systems are typically based on either anatomical structures (Denis Three-Column System) or on proposed mechanisms of injury (Ferguson and Allen, and the AO system)[1,9]. Overall, however, there is a paucity of strong data supporting the use of any of these systems. Additionally, there is currently no clear consensus regarding the optimal system for characterizing thoraco-lumbar fractures. An ideal system must be simple and reproducible based on commonly identified clinical and radiographic parameters. Current systems are either excessively convoluted, with an impractical number of variables, or are too simple, lacking sufficient detail to provide clinically relevant information. These limitations have yielded classification systems that are difficult to implement, have shown in-sufficient validity and reproducibility, and have not been widely popular[10-13]. The TLICS has been described and validated to address the shortcomings of the prior classification systems. The purpose of this paper is to review the TLICS system and to demonstrate its clinical application using 3 cases of thoraco-lumbar spine trauma.

Materials & Methods:

The study was carried out in the department of Neurosurgery, Bangabandhu Sheikh Mujib Medical University, Dhaka. The study was undertaken during January 2010 to July 2012.

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 included in the study.

Results:

Table-I

Distribution of patients by sex

Sex	Number	Percentage
Male	13	86.66
Female	2	13.33

Table-II

Distribution of patients by age (N=15)

Age in years	Number	Percentage
1-20	06	40.0
21-40	06	40.0
41-60	02	13.33
> 61	01	6.67
Total	15	100.00

Table I showed the distributation of male and female were 86% and 13.33% respectively From Table II, it was evident that age group of 1-20 years and 21-40 years, belonged to the highest group.

Table-III

Distribution of patients by causes of compressive fracture (N=15)

Causes	Number	Percentage
Fall from height	08	53.33
Road traffic accident	04	26.67
Fall of heavy object on back	02	13.33
Pathological fracture	01	6.67
Total	15	100.00

It was found (Table III) that the commonest causes of occurrence were fall from height in 8(53.33%) cases.

Table-IV

Distribution of patients by site of compression (N=15)

Site	Number	Percentage
L_1	09	60.0
D_{12}	05	33.33
L_2	02	13.33
Total	15	100.00

It was evident that (Table IV), the commonest site of compression was at L_1 vertebrae (60%), followed by D_{12} fracture (33.33%).

Table-V

Distribution of patients by the types of injury (n=15).

Type	Number	Percentage
Wedge fracture	9	60.00
Burst fracture	3	20.00
Seat belt injury	2	13.33
Fracture dislocation	1	6.67

It was documented that (Table V), the commonest fracture type was wedge fracture 9(60%).

Table-VI

Distribution of patients by type of weakness and outcome (N=15)

Clinical features	Number	Percentage
Paraparesis	13	86.66
Monoparesis	02	13.33
Bladder dysfunction	13	86.66
Bladder & Bowel dysfunction	03	20.0
Sexual dysfunction	02	13.33
Bowel dysfunction	02	13.33
Bladder, Bowel & Sexual dysfunction	02	13.33
Autonomic Function intact	01	6.67

Table VI, showed that the most of the sufferers had paraparesis (86.66%), the remaining 13.33% had monoparesis. The result revealed that the most of the patient (86.67%) had suffered from bladder dysfunction.

Table-VII

Distribution of the patients by complication of surgery (n=15)

Complication	Number	Percentage
Wound infection	03	20.0
Per operative bleeding	01	6.67
Respiratory distress	01	6.67

It was found that (Table VII), 20% of patients had wound infection and were treated by proper antibiotics and wound dressing.

Table-VIII

Distribution of the patients by outcome after surgery (n=15)

Improvement	Number	Percentage
Partially improved	10	66.67
Completely improved	04	26.66
No improvement	01	6.67

It was documented that 13(93.34%) of the patients improved after surgery (Table VIII).

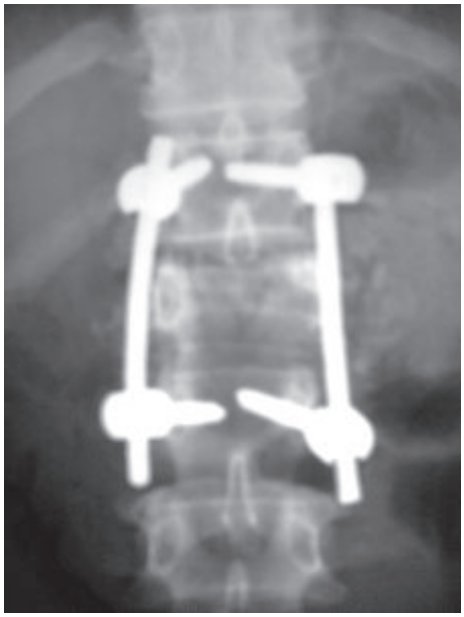

Fig.-1: *Posterior fixation of L1 fracture with pedicle screw and rod.*

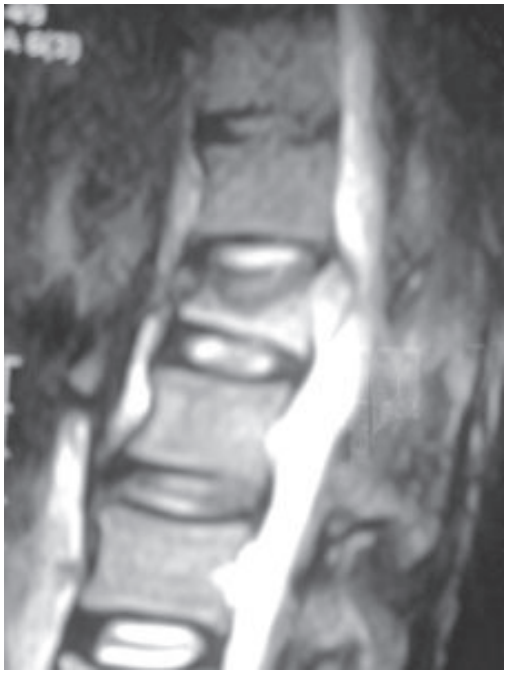

Fig.-2: *L1 compression fracture*

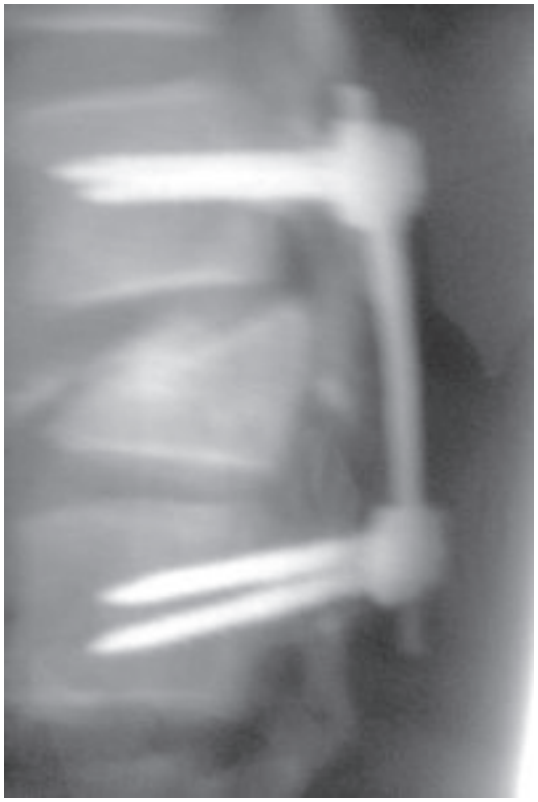

Fig.-3: *Lateral view of posterior fixation of L1 fracture with pedicle screw*

Fig.-4: *Clinical improvement of patients after posterior fixation*

Discussion:

Exact evaluation of the pedicles is an essential pre-requisite for posterior plating and the application of fixator systems. The pedicles are short conical tubes with an oval cross-section. The objective is to insert the screws through the center of the pedicles, approximately parallel to the upper end plates or angled downward. The screws should be aimed towards the midline to an end plate or to be angled downward. The screws should have coverage towards the midline to a certain extent, up to 20% depending on the spinal level, in order to ensure that they do not penetrate the lateral wall of the vertebral body. The long axis of the pedicle can be identified either by direct exposure or by image intensification. Although each method is reliable by itself, it is best to use a combination of the two. In addition, there are other aids for deciding screw position which are useful particularly when the anatomic landmarks are difficult to define due to distorted anatomic relationships[14].

At thoracic Spine, the point of entry is just below the rim of the upper facet joint, 3 mm lateral to the

center of the joint near the base of the transverse process. This screw should be angled 7-10^{o} towards the midline and 10- 20% caudally[14].

At lumbar spine, practically at all levels, the long axis of the pedicle pierces the lamina at the intersection of two lines: a vertical line tangential to the border of the superior articular process, and horizontal line bisecting the transverse process. Their point of intersection lies in the angle between the superior articular process and the base of the transverse process (Fig. 1). The screws should be converged by 5^{0} at the thoraco-lumbar junction and by 10-15^{0} as one progress form L2 - L5[14].

Proper placement of screws in the sacrum is difficult because of its variable anatomy. The screws may be introduced a different points and in different directions, depending upon the instrumentation and the quality of the bone. In general, the entry point is located at the intersection of two lines: a vertical line tangential to the lateral border of the S1 facet and a horizontal line tangential to the inferior border of this facet. In most cases, the screws converge towards the midline and aim towards the anterior corner of the promontory. An alternative possibility is to insert the screws more sagitally or parallel to the sacroiliac joint. The entry point shifts slightly medially as the screw direction diverges. Screws inserted parallel to the sacroiliac joint aims towards the anterior superior angle of the lateral mass of the sacrum. When positioning screws in the sacrum so as to achieve optimal purchase, it is necessary to note the density of the bone - the subchondral bone is the strongest, whereas the lateral mass of the sacrum is often very osteoporotic, some-times even hollow[14].

In any case, anteroposterior (AP) and lateral preoperative X-rays are indispensable. If there is any suggestion of anatomic variations, then CT scans are essential. They give information about pedicle diameter and direction; intraoperatively, the use of image intensification is indispensable, too. It confirms the location and direction of the screw. In every difficult case, intraoperative myelography with image intensification helps to identify the medial border in relationship to the nerve root[14].

At the lumbar spine, the inferior and inferior lateral aspect of the pedicle can be exposed by dissecting subperiosteally from the base of the transverse process anteriorly. The soft tissues with the spinal nerve and blood vessels were carefully retracted with a curved dissector. A small curved dissector is used to probe the lateral wall of the pedicle. If necessary, the inferior part of the medial wall may also be probed. In addition, osteotomy of the base of the transverse process can help to identify the pedicle. Alternatively, the spinal canal can opened and the medial wall of the pedicle identified. The latter two techniques are usually not necessary in routine pro-cedures. At the sacral level, it is very helpful to ex-pose the S nerve root, which allows visualization of the lateral wall of the spinal canal[15].

Alter identification of the entry point and the direction of the pedicle, the posterior cortex is perforated for approximately 5 mm using a 3.5-mm drill, preferably with the oscillating attachment. Continued drilling of the pedicle can be dangerous. A safer technique is to prepare the entry points with the pedicle awl and to open the pedicle with a pedicle feeler. This preparation is per-formed to the junction between the pedicle and vertebral body. The circumference of the canal is checked with the tip of the AO depth gauge, which has an angled tip to ensure that perforation of the bone has not occurred; particularly medially. Image intensification with the gauge or a Kirschner wire in place confirms the proper position. The depth gauge may be inserted into the cancellous bone of the vertebral body and the anterior cortex is not perforated. If there is doubt regarding the depth, take a lateral radiography and ensure that the depth gauge does not penetrate more than 80% of the AP body diameter, then the anterior cortex will not be perforated[16].

In previous study the average age group were 37 years (± 11.7 years), there were 9(69%) male patients and 4(31%) female patients. The average follow-up period was 30 months (± 13.5 months)[16]. In our study the highest age group were 1-20 years and 21-40 years that was 6(40%). It was evident that 13(86.66%) were male and 2(13.33%) were female. In previous study 10 patients sustained unstable burst fractures and 3 patients sustained translational injuries (fracture-dislocation)[16]. In our

study 9(60%) were compressed fracture, 3(20%) (Fig. 2 and 3) were unstable burst fracture and 1(6.67%) were fracture dislocation. Surgery was performed as early as possible, provided the patients were fit for surgery. In previous study four patients experienced massive bleeding of more than 3,000 ml, and three of them sustained combined injuries, such as extremity fractures or internal organ injuries requiring surgery[16]. In our study 5(33.33%) patients had dural tear.

Among the 13 study patients, neurological improvement was observed in 12 (92%)[7]. In our study (Fig. 4) clinical improvement occurs in 14(93.33%) of patients.

Conclusion:

Patient with incomplete spine injury showed good to excellent recovery and could be mobilized early with external support by pedicle screw fixation. So early surgery with posterior decompression and fusion and fixation can improved the patients neurological function.

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Early Post-operative Visual Outcome in Patient with Pituitary Adenoma

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Abstract:

Background: *Pituitary adenoma, which accounts for 17.4% of all brain tumors, is the third most frequently diagnosed brain tumor, following intracranial glioma and meningioma. The visual disturbance in pituitary adenoma ranged from blurring of vision with or without headache to total loss of vision. In patients with visual field defects, bitemporal hemianopia was the commonest visual field defect. Early improvement of visual function is one of the major indication surgery.* ***Objective:*** *The purpose of this study was to comparison between the pre and post-operative visual parameters and to find out the value in assessment of the prognosis of early postoperative visual function and also to find out the factor which influence the early post-operative visual outcome.* ***Methods:*** *A prospective study was done from September 2010 to April 2012 in the department of neurosurgery, Bangabandhu Sheikh Mujib Medical University, 30 cases of pituitary adenoma had been included in this study of those who were presented with visual symptoms. Visual assessment was done before the operation and outcome was analyzed at discharged from hospital.* ***Results:*** *Within 60 eyes, 13 (43.3%) patients presented with blindness of one or both eyes. 10 (33.3%) presented with uniocular and 3 (10.0%) presented with binocular blindness. Duration of the symptoms ranged from 2 months to 48 months. Patients underwent either transcranial or transsphenoidal tumor decompression. At discharge out of 30 patients, 23 (76.7%) showed improvement, 2 (6.6%) patients were deteriorated post-operatively. P value was <0.001, in z 'test', Z=91.5, which was highly significant. Post-operative visual status was analyzed with age, sex, duration of symptoms, suprasellar extension, and methods of surgery and extent of tumor resection to find out that any other factor influenced the visual outcome. In bivariate analysis it was shown that only duration of the symptoms only other factor that influenced the visual outcome (statistically significant, p value 0.017).* ***Conclusion:*** *With this study it was statistically proved that pre-operative visual status is the main factor for improvement of early post-operative visual outcome in pituitary adenoma and duration of symptoms had also influence the early post-operative visual outcome. Duration less than 12 months had a favorable outcome.*

Key words: *Pituitary Adenoma, Visual Acuity, Visual Field, Bitemporal Hemianopia, Optic atrophy*

Abbreviation: *VF (visual field), FA(visual aquity)*

Introduction:

Pituitary adenoma, which accounts for 17.4% of all brain tumors, is the third most frequently diagnosed brain tumor, following intracranial glioma and meningioma[1]. They are more common in adults, comprising 2% of all adenomas in children[2]. Inappropriate pituitary hormone secretion and visual field deficits are the most characteristic presenting features of pituitary adenomas. Less specific symptoms such as headache, and subtle signs of pituitary hormone deficiency with peripheral endocrine organ hypofunction characterized by amenorrhea, loss of libido, and lethargy, are also common[3]. The visual disturbance in pituitary

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adenoma ranged from blurring of vision with or without headache to total loss of vision. In patients with visual field defects, bitemporal hemianopia was the commonest visual field defect. The reason for such a wide range of visual problems lies in the anatomical variation in the location of optic chiasma and due to the special arrangement of optic nerve fibers in the chiasma[4]. Visual impairment is a major indication for surgical intervention, by the transcranial or transphenoidal route[5]. The quality of postoperative results is encouraging, but there are still too many patients whose vision does not return to normal. Postoperative visual recovery is greatly influenced by the degree of preoperative visual loss, the duration of visual symptoms and suprasellar extension of the tumor. Integrity of the vascular supply to the chiasm and optic nerves is probably the primary prerequisite for visual recovery[6]. Improvement in visual function has been postulated to occur in three stages: rapid recovery within minutes to a couple of days, delayed recovery over weeks to months, and late recovery over months to years. Improvement in vision may take place immediately after decompression, and visual evoked potentials have been documented to improve within 10 minutes of decompression. It has been postulated that the initial improvement is the result of the removal of a physiologic conduction block. Further improvement during a stage of delayed recovery is thought to be the result of remyelination of the decompressed optic pathways. Finally, late recovery of visual field over months to years has not been well studied. Most studies of improvement of visual function after treatment of pituitary tumors compressing the anterior visual pathways have compared pre-operative visual function with visual function at a single postoperative visit. Some studies have reported improvement in visual function using kinetic perimetry between the first week of surgery and a later visit[7].

This study was done, with the comparison between pre and pot-operative visual parameters to find value in assessment of the prognosis of postoperative visual function and also to find out the factor which influence the visual outcome. An assessment of pre-operative visual acuity, field scores, age of the patient, presence or absence of optic atrophy, duration of the symptoms and size or volume of the tumour with the help of neuro-imaging, methods of surgery, presence of pituitary apoplexy, extent of tumour resection to ascertain correlation with the post-operative visual outcome will also be made.

Materials and Methods:

Between September 2010 to May 2012, 30 patients (60 eyes) were selected in the department of Neurosurgery, BSM Medical University, who were diagnosed as pituitary adenoma by imaging presented with visual symptoms and underwent surgery either transcranial or transsphenoidal approach according to the inclusion and exclusion criteria.

Inclusion criteria

Patients with neuro-images suggesting pituitary adenoma. Patient with pituitary adenoma who had visual impairment and requiring surgery for it. Patient who had post-operative histological confirmation of pituitary adenoma.

Exclusion criteria

Patients who had concomitant intra-ocular disease making visual assessment difficult. Systemic disorders other than pituitary adenoma that affected visual function. Presence of any other intracranial pathology

All cases were confirmed as pituitary adenoma by surgery and histopathology. Pre-operative and post-operative visual status were analyzed and documented. Post-operative visual status was analyzed at discharged from hospital. Those patients whose data were not collected after operation had been excluded in this study. Data regarding age; sex; duration of symptoms; mode of presentation; and visual acuity and visual field status at admission and at discharge from hospital were documented. Visual acuity was recorded using the Snellen chart. Visual field charting was performed using Octopus or Humphrey visual field analyzer and fundus examination by ophthalmoscope were done and documented.

The multifactorial effect of variables such as age, sex, duration of visual decline, duration of blindness, imaging characteristics of sellar or parasellar extension, extent of resection was studied on the visual outcome.

Data were analyzed in SPSS (version 17). The test statistics used to analyze the data were descriptive statistics and Chi-square probability test and the level of significance was set at 0.05.

Results:

Table-I

Showing the age distribution of the patients (n=30)

Age group in year	Number of patients	Percentage
11-20	2	6.7
21-30	12	40.0
31-40	8	26.7
41-50	4	13.3
51-60	2	6.7
>60	2	6.7
Mean ±SD	36.2±13.7	
Range (Min-Max)	(16-70)	

30 cases of pituitary adenoma had been included in this study those who were presented with visual symptoms. Pituitary adenoma was diagnosed pre-operatively by MRI and after operation confirmed by histopathology. The age distribution of 30 patients ranged from 16-70 years with a mean ±SD of age was 36.2±13.7. The patient age distribution shows a peak incidence between 26– 40 years for pituitary adenoma. Male had slightly preponderance than female in this series with male to female ratio 1.1:1 (Table I).

All patients presented with visual problems (100.0%). Majority (93.3%) patients presented with headache, 5 patients (16.7%) presented with acromegaly, 1 patient (3.3%) presented with gigantism, 5 patients (16.7%) presented with amenorrhea and 2 patients (6.7%) presented with gynaecomastia and erectile dysfunction, only 1 patient (3.3) presented with diabetes insipidus.

Table-II

Distribution of visual symptoms among 30 patients (n=30)

Visual symptoms	Frequency (n=30)	Percentage (n=30)
Blurred vision	17	56.7
Vision loss	13	43.3
i) One eye	10	33.3
ii) Both eyes	3	10.0

Among 30 patients 17 presented with blurred vision (56.7%). 13 (43.3%) patients presented with loss of vision, among them 10 (33.3%) presented with loss of vision on one eye and 3 (10.0%) patients presented with loss of vision on both eyes (Table II).

Duration of the symptoms ranged from 2months to 48 months. Majority (40%) had more than 12 months duration. Mean duration of symptoms were ±SD 16.3±16.0 (months).

Volume of the tumour ranged from 3-136.5 ml with a mean±SD was 28.4±33.4. Majority of the tumor were within 3-10 ml.

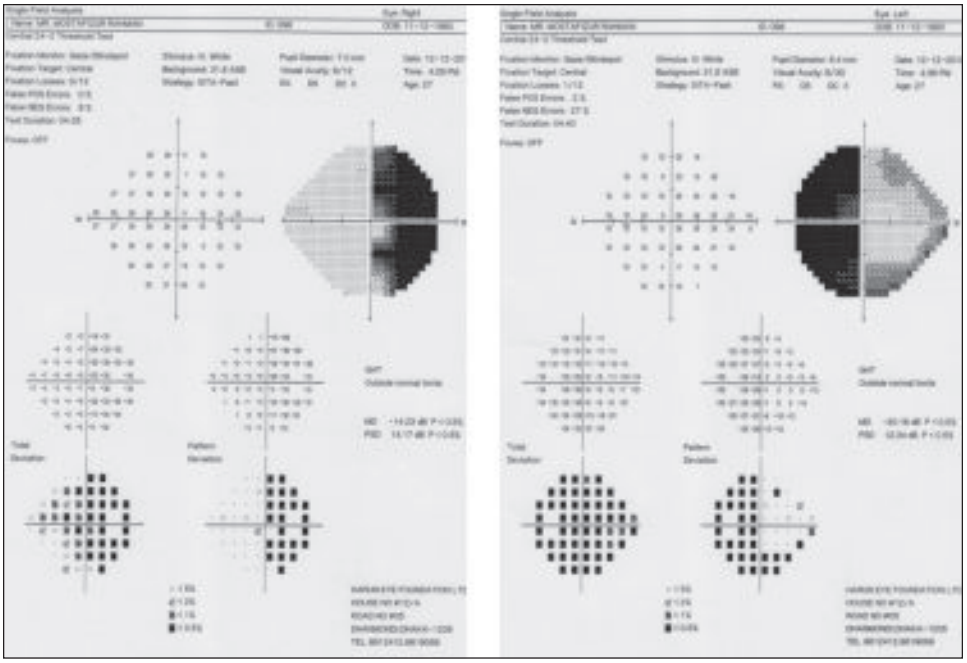

Fig.-1: *Visual field (VF) by Humprey visual field analyzer showing bitemporal hemianopia.*

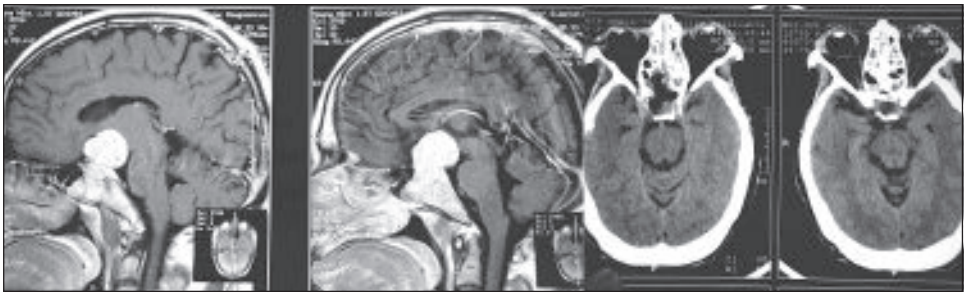

Fig.-2: *Showing a pituitary adenoma before and after surgery (Where gross total excision was achieved with pure endoscopic surgery)*

Pre-operative visual status were taken and documented. Regarding visual acuity - majority of the patients are within 6/6-6/36. Regarding VF majority were presented as bi-temporal hemianopia. 30% of eyes had optic atrophy (Figure 1).

Patient were underwent surgery by both transcranial and transsphenoidal route as surgeon's choice and also due to extension of tumor. 7 (23.3%) patients were underwent transcranial and 23 (76.7%) patients were underwent transsphenoidal approach. Gross total removal was achieved in 13 (43.3%) patients, near total in 14 (46.7%) patients and partial in 3 (10.0%) (Figure 2).

Visual Outcome

Post-operative VA, VF, status of the fundus and status of the colour vision of the eye were collected

Table-III

Correlation between pre-operative and post-operative visual acuity according to the no. of the eyes (n=60)

Pre-operative visual acuity (VA)		Post-operative visual acuity						p-value
		Improved		Stable		Deteriorated		
	Total	No.	%	No.	%	No.	%	
6/6-6/12	22	6		27.3	16	72.7	1	4.6
6/18-6/36	15	12	80.0	2	13.3	1	6.7	0.005
6/60-NPL	23	7	30.4	15	65.3	1	4.3	
Total	60	24	40.0	33	55.0	3	5.0	

χ^2= 14.707, df =4, P value reached from chi square test

Table-IV

Correlation between pre-operative and postoperative visual field according to the no. of the eyes (n=60)

Pre-operative visual field (VF)		Post-operative visual field						p-value
		Improved		Stable		Deteriorated		
	Total	No.	%	No.	%	No.	%	
Normal Field	2	-	-	2	100.0	-	-	0.413
Quadrantanopia	3	3	100.0	-	-	-	-	
Hemianopia	27	10	37.0	14	51.9	3	11.1	
Three quardrant field defect	23	9	39.1	14	60.9	-	0.0	
Atypical field defect	5	3	60.0	2		40.0	-	-
Total	60	25	41.7	32	53.3	3	5.0	

χ^2= 8.211, df=8, NS=Not significant, P value reached from chi square test

at discharge from hospital and were documented. It was compared with the pre-operative status.

Regarding visual acuity 24 (40%) eyes out of 60 eyes improved post-operatively, including 8 eyes whose vision were normal pre-operatively, 33 (55%) eyes remained stable, and 3 (5%) eyes deteriorated post-operatively. We compared the pre and post-operative data and found that visual acuity less than 6/36 improved better (statistically significant, p value 0.005) (Table III).

Regarding VF post-operatively, 41.7% eyes were improved; unchanged or stable were 53.3% and 5% of eyes were deteriorated. These were not statistically significant. We discussed why it was not statistically significant. But it was a good indicator that VF functions improved later on, because improvement of visual field is a continuous process, up to 2 years it can improve (Table IV).

In this study series, optic atrophy was presented in 30% of eyes. Optic disc pallor or atrophy was not a good predictive factor for visual outcome. Improvement or even complete regression of visual deficit often occurred in cases with preoperative optic disc pallor or atrophy. In this series, the study showed that pre-operative optic atrophy had a worse prognosis for visual outcome post-operatively (statistically significant, p value 0 .0001).

Table-V

Post-operative visual status of 30 patients (n=30)

	No. of the patients(n=30)	Percentage (n=30)
Improved	23	76.6
Stable	5	16.7
Deteriorated	2	6.7

p <0.001, in z 'test' (highly significant) Z=91.5

Post-operative visual status categorized into improvement, stable and deteriorated. Improvement means improved any of the VA, VF, and fundus or colour vision. Deterioration means deteriorated of any of the VA, VF, and fundus or colour vision. Stable means those who didn't improve any of the VA, VF, fundus or colour vision. Out of 30 patients, 23 (76.7%) showed improvement, 2 (6.6%) patients were deteriorated post-operatively. P value <0.001, in z 'test', Z=91.5, which is highly significant (Table V).

We analyzed the post-operative visual status with age, sex, duration of symptoms, suprasellar extension, and methods of surgery and extent of tumor resection to find out that any other factor influenced the visual outcome. In bivariate analysis it was shown that only duration of the symptoms only other factor that influenced the visual outcome (statistically significant, p value 0.017).

So with this study it was statistically proved that pre-operative visual status is the main factor for improvement of post-operative visual outcome in pituitary adenoma, duration of symptoms has also influence the visual outcome. Duration less than 12 months have a favorable outcome.

Discussion:

The final study subjects were 30 patients of pituitary adenoma all of them presented with visual symptoms and was recruited according to the exclusion and inclusion criteria. The visual outcome in this study was analyzed as improvement over preexisting vision at admission. Successful surgical treatments of pituitary adenomas resulting in recovery and in many cases normalization of visual functions were found in this series of patients. In our series we assessed visual status after 7 days of surgery and compared with the pre-operative status of the patients and also correlated with other factors that influenced it. Kerison et al. 2000[7] observed statistically significant improvement in visual status at surgery to one week, Marcus et al. 1991[8] also observed significant improvement of visual function within one week of surgery.

All patients presenting with visual symptoms of pituitary adenoma were included in this study. 13 (43.3%) presented with blindness of one or both eyes. 10 (33.3%) patients presented with uniocular and 3 (10.0%) patients presented with binocular blindness. Ebersold et al. 1986[9] found 72 patients out of 100 presented with loss of vision, another series Elgamal et al. 2007[10] found 17% eyes presented with loss of vision due to pituitary adenomas.

Duration of visual disturbances ranged from 2 months to 48 months with a mean duration 16.3 months.

The easiest and most reproducible method of evaluation and follow-up of visual function is corrected VA and VF. In our series we evaluated the pre-operative visual acuity and compare with the post-operative results. 8 eyes had normal visual acuity before operation and they didn't deteriorated after operation. 24 (40%) eyes out of 60 eyes improved post-operatively, including 8 eyes whose vision were normal pre-operatively, 33 (55%) eyes remained stable, and 3 (5%) eyes deteriorated post-operatively. We compared the pre and post-operative data and found that visual acuity less than 6/36 improved better (statistically significant, p value 0.005). These findings are consistent with those of other authors, reporting post-operative improvement of VA in 32–81% of the patients, and no improvement or worsening in 18–68% of the patients [11].

Post-operatively, VF in 41.7% eyes improved; was unchanged or stable in 53.3% and 5% of eyes deteriorated. These findings are not in accordance with those of other authors reporting postoperative improvement of VF in 75–92% and no improvement or worsening of VF in 8–19% of the patients[11]. This is due to our early visual field assessment of the patient than the other authors and needs of long term follow-up. Improvement of visual field defects is a continuing process for at least 1 year [12, 5, 7]. Kerrison et al. 2000[7], showed progressive improvement of visual fields even more than 2 years after surgical decompression of the optic chiasm. Jacob et al. 2009[13] found that their initial VF defects after surgery did not reach statistical significance. But this is a good indicator to show that the improvement of VF function will occur later on.

In this study series, optic atrophy was presented in 30% of eyes. Optic disc pallor or atrophy was not a good predictive factor for visual outcome. Improvement or even complete regression of visual deficit often occurred in cases with preoperative optic disc pallor or atrophy[14]. In this series, the study showed that pre-operative optic atrophy had a worse prognosis for visual outcome post-operatively (statistically significant, p value 0 .0001).

Overall outcome in 30 patients after surgery 76.7% showed mild to moderate improvement, 16.7% showed unchanged and 2 patients (6.7%) showed deterioration. This was compared with other studies (table VI) and the result was the same as others.

Table-VI

Summary of the results of pituitary macroadenoma surgery reported in the literature

Authors and year	No. of the patients	Improved (%)	Not improved (%)
Fahlbusch et al. 2001[15]	44	92	8
Mortini et al 2005[16]	289	92	8
Nimsky et al. 2006[17]	106	64	36
Dehdashti 2008[18]	80	89	11
Anik et al 2011[19]	72	80	20
Current series	30	76.7	23.3

A variety of prognostic factors have been studied in patients with compressive pituitary adenomas. Gnanalingham et al. 2005[5] stated that age, optic disc pallor and duration of symptoms were found to be predictive of the visual outcome. Marcus et al. 1991[8] stated that age and optic disc pallor were found to be predictive of the post-operative visual outcome. Nakao and Itakura 2011[20] found that only duration of visual disturbance significantly affected the visual outcome. Messerer et al. 2011[21] didn't find any predictive factor that significantly affected the outcome. In this series age, sex, duration of symptoms, volume of the tumours, suprasellar extension, methods of surgery, extent of tumor resection were analyzed with the visual outcome. Bivariate analysis showed that only duration of visual disturbances was the only other factor that affected the post-operative visual outcome. Duration less than 12 months had a better outcome than duration more than 12 months (statistically significant, p value <0.017).

The improvement of visual dysfunction after surgical treatment is supposed to consist of two, or probably even three, phases. There is an early phase, comprising the first hours and days after surgery. In this early fast phase, the improvement is caused by decompression of the visual pathways, leading to a restoration of signal conduction. Visual recovery has been demonstrated in the first days after surgical treatment. The second phase, i.e., delayed recovery, is pathophysiologically caused by restoration of axonal transport and remyelination,

and based on remyelination of the optic nerve. This phase of delayed recovery may last for several years[7]. A precise boundary between the end of the fast phase of recovery and the start of the delayed recovery seems to be artificial, because these two phases reflect different pathophysiological mechanisms, which may co-exist for a certain time-period. The contribution of the fast phase of recovery might be larger [5]. For this reason in this study series visual outcome was analyzed within one week of surgery, which is a good indicator that visual improvement will occur later on.

Conclusion:

In this study we have found that the better pre-operative visual status is the main parameter for visual outcome in patient with pituitary adenoma. If patient's ophthalmological status is better pre-operatively his visual outcome will be better after surgery in pituitary adenoma. We also found that duration of symptoms influence the visual outcome. Duration less than 12 months have a favorable outcome.

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REVIEW ARTICLE

Neuropathy in Chronic Renal Failure

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Abstract:

Peripheral neuropathy is common in chronic renal failure patients and it's early detection and treatment reduces the sufferings of these patients. Studies of neuropathy in ESKD have demonstrated prevalence rates which vary from 60 to 100%. The striking pathologic features of peripheral neuropathy in patients of CRF are axonal degeneration in the most distal nerve trunks with secondary segmental demyelination. The most frequent clinical features are those of large-fiber involvement, with paresthesias, reduction in deep tendon reflexes, impaired vibration sense, weakness and muscle wasting. Patients of CRF may present with mononeuropathies or autonomic failure also. The exact cause of nerve involvement has not been identified but the middle molecule hypothesis is widely accepted. Dialysis in any form fails to improve the neuropathy but renal transplantation does improve the neurological complications. This review details the various features of neuropathy in patients of chronic renal failure.

Keywords: *Neuropathy; Chronic renal failure, Middle molecule hypothesis.*

Abbreviations: *CRF – chronic renal failure; CTS – carpal tunnel syndrome; EMG – electromyography; EPO – erythropoietin; ESKD – End stage kidney disease; GFR – glomerular filtration rate; NSS – neuropathy symptom score; PTH – parathyroid hormone.*

Introduction:

Neuropathy is a common problem in patients of chronic renal failure (CRF). It increases the suffering of the patients who are already burdened by the renal problem. The increasing prevalence of CRF has also increased the load of patients with peripheral neuropathy. Early recognition of neuropathy in patients of CRF and appropriate treatment of the condition may decrease the suffering of these patients. Peripheral neuropathy in patients with CRF was suspected in the late 19th century. The possibility of peripheral neuropathy in patients treated with hemodialysis was first raised shortly after the introduction of the first formal hemodialysis program. Since the introduction of hemodialysis and renal transplantation in the early 1960s, uremic neuropathy had been investigated thoroughly.The first clinical documentation of neuropathy was provided in 1961 in two young male patients with hereditary interstitial nephritis and deafness[1]. Asbury, Victor and Adams published two articles titled 'Uremic polyneuropathy' in 1962[1] & 1963[2] in which they stated, "The fact that chronic renal failure may be associated with polyneuropathy is not generally appreciated and is practically undocumented in the medical literature." They extensively described clinical and pathological findings in four men who developed neuropathy as a consequence of CRF of varying etiologies. All four patients had clinical features of renal disease for many years before the development of neuropathy, which manifested as a symmetrical length dependent sensory motor neuropathy. Nerve biopsies established axonal degeneration, maximal distally, with sparing of the proximal nerve segments and nerve roots. Moreover, there was no evidence to suggest nerve compression, inflammation or superimposition of

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a systemic disease process, such as diabetes or amyloid, leading to conclusion that the development of neuropathy was a consequence of the underlying renal disorder.

In 1964, Preswick & Jeremy[3] described presence of subclinical polyneuropathy in patients with renal insufficiency. In 1971, Dyck and colleagues[4] established the current concept of uremic neuropathy based on their extensive nerve conduction studies in vivo and in vitro and on light and electron microscopy study. Using quantitative histology, they demonstrated axonal shrinkage. The dysfunction of the neuron, rather than the schwann cells, resulted in a decrease in the diameter of the axon, rearrangement of myelin, and finally, complete degeneration of the axon. Nielsen published numerous papers from 1970-1974[5,6] on clinical and electrophysiological studies in patients of chronic renal failure

Early clinical neurophysiological investigations in CRF patient demonstrated reduction in motor nerve conduction velocity in symptomatic and asymptomatic patients[7]. In studies of the natural history of uremic neuropathy, clinical and nerve conduction findings were compared amongst patients treated conservatively and those receiving dialysis therapy. Whereas the development of neuropathy in conservatively treated group was related to deteriorating renal function, those patients treated with long term dialysis manifested improvement in both clinical and neurophysiological parameters. Following these early reports and in light of the increasing use of dialysis and renal transplantation therapies, greater attention was focused on uremic neuropathy, with numerous studies reporting high rates of neuropathy in CRF patients, generally relating the development of neuropathy to the severity of renal failure.Studies by Bolton[7,8] in 1970s demonstrated nerve conduction slowing in renal failure patients as well as improvement in neurophysiological parameters following renal transplantation.

Incidence and Clinical Features of Neuropathy in CRF

Peripheral neuropathy in end-stage kidney disease (ESKD) presents as a length-dependent, distal sensorymotor symmetrical polyneuropathy with greater lower limb than upper limb involvement[9]. Studies of neuropathy in ESKD have demonstrated prevalence rates which vary from 60 to 100%, depending on the choice of nerve segments, the indices measured and the number of nerves studied[10-21].

The condition is of insidious onset, progressing over months, and has been noted to have a male predominance. It generally only develops at a glomerular filtration rate of less than 12 ml/min[9].The neuropathy usually evolves over several months but rarely an acute or sub acute course is seen[10]. Although usually mixed motor and sensory in type, cases of either pure sensory or pure motor have been reported. The most frequent clinical features are those of large-fiber involvement, with paresthesias, reduction in deep tendon reflexes, impaired vibration sense, weakness and muscle wasting.

Laaksonen et al[18] staged the clinical severity of uremic neuropathy in 21 CRF patients. He used a modified version of neuropathy symptom score (NSS) and combined this assessment with results of nerve conduction studies. The NSS quantified symptoms that were grouped into three categories to reflect alteration in motor, sensory, and autonomic systems. Within each group, further subsets were used to group symptoms according to the region affected and the presence of positive or negative symptoms. Using the NSS and the staging procedure previously used in studies of diabetic patients, 81% of CRF patients received a diagnosis of neuropathy. Stage 1 neuropathy (asymptomatic neuropathy), was diagnosed in 19%, stage 2 neuropathy (symptoms non disabling) was present in 48% and stage 3 neuropathy (disabling symptoms) was noted in 14%. Krishnan et al[11] in another study showed that 93% of CRF patients had neuropathic changes on NSS testing, with 72% diagnosed with stage 2 neuropathy and 21% with stage 3 neuropathy, despite all patients meeting currently accepted guidelines of dialysis adequacy.

Typical uremic neuropathy symptoms are insidious in onset and consist of a tingling and prickling sensation in the lower extremities.

- Paresthesia is the most common and usually the earliest symptom.
- Increased pain sensation is a prominent symptom.
- Weakness of lower extremities and atrophy follow the sensory symptoms. As disease progresses, symptoms move proximally and involve the upper extremities.
- Muscle cramps and restless legs syndrome were also seen in uremic patients without neuropathy. Patients report that crawling, prickling, and itching sensations are felt in their lower limbs which are partially relieved by movement of the affected limb.
- Autonomic dysfunction is present and usually manifest as postural hypotension.
- A Guillain-Barre type of presentation is rare, but rapidly progressive course with respiratory failure has been reported[18].
- Cranial nerve involvement is rare.

The vestibulocochlear nerve is the most commonly affected cranial nerve in uremia. Variable hearing loss and occasionally complete deafness are reported, which may reverse with dialysis or renal transplantation. Uremia related hearing deficit must be distinguished from the ototoxic effects of aminoglycoside antibiotics and other drugs, as well as conditions associated with hereditary hearing loss and nephropathy.

Impaired vibratory perception and absent deep tendon reflexes are the most common clinical signs reported by Lindbolm and Tegner[12]. Yosipovitch et al[13] found paradoxical heat sensation in the feet of 42% of patients with chronic renal failure as compared to less than 10% of healthy controls. Muscular weakness and wasting were observed in 14%.Focal weakness, sensory loss, and positive tinel sign at compression sites can be observed in the median, ulnar, or peroneal nerve distribution if compressive mononeuropathy is present. Abnormal valsalva maneuver and orthostatic hypotension may be noted in patients with autonomic neuropathy. Uremic pruritus has been shown to be associated with altered sympathetic innervations of the skin and this correlated with impaired peripheral somatosensory nerve conduction, suggesting that uremic pruritus is a manifestation of uremic neuropathy[14].

Mononeuropathies in CRF

Mononeuropathies are a frequent clinical complication in CRF patients and most typically occur in the median, ulnar, and femoral nerves. In uremia susceptibility of the peripheral nerves to compression and local ischemia is increased[15]. Carpal tunnel syndrome (CTS) is the most common mononeuropathy in CRF, with prevalence rates varying from 6% to 31%[16]. The carpal tunnel syndrome is caused by entrapment of the median nerve in the carpal tunnel, which is formed by the flexor retinaculum and the carpal bones. Symptoms include burning pain and paresthesias involving the ventral surface of the hand and fingers I-III and lateral half of finger IV. Thenar muscle atrophy may occur. Renal transplantation relieves the symptoms but does not reverse the atrophy[17]. B_2-microglobulin amyloidosis is a major factor underlying the development of CTS in CRF patients, a complication noted in patients on long term hemodialysis. Amyloid deposits have been identified in synovial specimens from dialysis patients with CTS and an increase in the rate of CTS has been demonstrated with increasing hemodialysis duration. Strategies geared at reducing the levels of B_2-microglobulin, such as the use of high-flux biocompatible membranes and B_2-microglobulin adsorption columns, have resulted in reduced rates of CTS development and ultimately improvement in symptoms.Other factors that may contribute to the increased incidence of CTS in CRF patients include uremic tumoral calcinosis and the placement of arteriovenous fistulas, inducing a “steal” of blood from the distal limb. This may also increase the venous pressure in the distal limb leading to nerve compression[18]. Damage to the ulnar nerve can occur by uremic tumoral calcinosis at the wrist, in Guyon’s canal. Depending on the site of compression in the canal, this may cause purely

motor dysfunction with paresis of intrinsic hand muscles, sensory loss to the hypothenar eminence, the small finger and the medial part of ring finger or mixed symptomatology. B_2 Amyloid deposition in the palm, can lead to local ulnar nerve compression with pain and paraesthesia over the fourth and fifth fingers.

Autonomic Neuropathy in CRF

Autonomic neuropathy may develop in CRF patients and can play a role in the pathogenesis of intradialytic and orthostatic hypotension, incontinence, diarrhoea, constipation, oesophageal dysfunction, hyperhydrosis and impotence[19,20]. In a study of 36 CRF patients, gastrointestinal autonomic symptoms were evident in 42% and impotence in 45%[21]. Although postural hypotension was an uncommon clinical finding, 36% of patients complained of episodes of postural dizziness, which was most prominent in elderly CRF patients.Some studies have suggested that autonomic neuropathy occurs as a manifestation of generalized polyneuropathy but others have shown no correlation between autonomic dysfunction and peripheral nervous system abnormalities[22].The mechanism underlying the development of uremic autonomic neuropathy remain unknown, although an association with hyperparathyroidism has been suggested.Studies utilizing objective measures of autonomic function, including R-R interval variation as a measure of parasympathetic function and sustained hand grip and sympathetic skin response as a measure of sympathetic function, have established abnormalities in upto 62% of CRF patients on dialysis treatment. However, these abnormalities frequently occur in the absence of clinical symptoms of autonomic dysfunction[23]. Parasympathetic dysfunction has been shown to occur with greater frequency them sympathetic dysfunction, which is generally more common in diabetic CRF patients[24-29]. Besides para-sympathetic vagal dysfunction neuropathy of other cranial nerves especially optic, trigeminal, facial and vestibulocochlear neuropathy have been described anecdotally[25]. The contribution of autonomic dysfunction to the development of intradialytic hypotension remains a matter of ongoing debate, with some studies suggesting a possible association and other suggesting no significant relationship[26]. A recent review of the literature on the use of the oral alpha-1-adrenoceptor agonist Midodrine in the treatment of intradialytic hypotension suggested a beneficial effect[27]. Autonomic neuropathy improves after institution of dialysis and resolves following successful renal transplantation. Although the etiology of hypotension during hemodialysis is multifactorial, one patient showed a paradoxical bradycardia in response to hypotension. Patients with autonomic dysfunction have been shown to have more cardiac arrhythmias during dialysis and are more prone to intradialytic hypotension.

Pathophysiology of Peripheral Neuropathy in CRF patients

The pathologic features of peripheral neuropathy in patients of CRF are striking axonal degeneration in the most distal nerve trunks with secondary segmental demyelination. The condition has a predilection for large diameter axons, with relative sparing of the unmyelinated and small myelinated afferent neurons. There is a marked loss of axons and fiber breakdown in the distal nerve trunks of the legs with less severe changes proximally, normal spinal roots and degeneration in the cervical portion of the dorsal column. Anterior horn cells are intact but may show chromatolytic changes. Paranodal demyelination and separation of the myelin sheath from the axolemma are also found, but are considered to be secondary to the primary axonal damage[28]. Although there may well be a defect in schwann cell function in uremia, the predominant defect is one of axonal loss with secondary demyelination. Following renal transplantation, early remyelination accounts for the initial rapid improvement in nerve conduction, whereas nerve regeneration is a slow process taking many months. Similarly, there is no significant improvement in nerve conduction studies following a single hemodialysis treatment[29]. In patients of chronic renal failure it was found that the number of myelinated fibers was approximately one half of normal at the mid calf level and only one third of normal at ankle level. In transverse electron microscope sections, most of the myelinated fibers of the uremic nerve had a normal appearance

except for irregularities of the myelin sheath, such as splitting of the myelin lamellae and separation of axolemma from compact myelin. Nerve biopsies also showed onion like structures due to several layers of schwann cell processes around myelinated nerve fibers, suggesting repeated episodes of demyelination followed by remyelination[30]. The precise cause of uremic neuropathy remain unknown although a number of potential neurotoxins accumulate in end stage renal disease. Functional and morphological alteration of peripheral nervous system in end stage renal disease predispose to the development of clinically manifest mono and polyneuropathies.

Mostly, the adverse effects on the peripheral nervous system are minimal as long as the glomerular filtration rate (GFR) exceeds roughly 12 ml/min., whereas the neuropathy is reversed, at least partially, by dialysis and dramatically by renal transplantation. At glomerular filtration rates below this value, nerve conduction studies become abnormal and patients begin to demonstrate clinical signs of peripheral nerve dysfunction when GFR of about 6 ml/min is reached[31]. The so called "middle molecule hypothesis" with accumulation of one (or several) neurotoxic molecules of molecular weight 300-2000 Daltons which are slowly dialyzable has been a popular explanation for the genesis of uremic neuropathy. But no one substance has yet been convincingly shown to have a close correlation among plasma and tissue concentrations and the severity of the polyneuropathy[32]. The observation that uremic neuropathy improves with hemodialysis has led most observers to conclude that neuropathy results from the accumulation of a dialyzable metabolite. It had been speculated that these substances might be in the middle-molecule range; compounds of this size cross most dialysis membranes much more slowly than smaller molecules such as creatinine and urea, which are the usual measures of chemical control of uremia. Thus, one might theoretically achieve chemical control of uremia, while failing to remove the putative toxins. Supporting this contention have been the observations that control of neuropathy may in some cases depend on increased hours of dialysis per week, beyond that which is necessary for chemical control of uremia; and that peritoneal dialysis appears to be associated with a lower incidence of neuropathy. These observations suggest that the peritoneal membrane may permit passage of some toxic molecules more readily and selectively than the cellophane membrane used in hemodialysis.

Because of the varying nutritional status of uremic patients, the possibility that vitamin deficiency is a mechanism of neuropathy should be considered. Massive doses of vitamins administered both orally and parenterally have failed to have any clear influence on the course of neuropathy in informal trials; this experience has led to the general agreement that uremic neuropathy is not a result of vitamin deficiency. However, patients who receive chronic hemodialyis require supplementation with at least the water-soluble vitamins to avoid depletion; failure to do so may lead to nutritional neuropathy, and occasionally to Wernicke's encephalopathy[33,34]. Many other factors, such as decreased transketolase activity, reduced circulating biotin concentration, increased concentration of phenols and myoenositol and hyperparathyroidism have been proposed in addition to thiamine deficiency. There may be an additional ischaemic component to uremic neuropathy as increasing the haematocrit with erythropoietin therapy improved nerve conduction studies.

Neuropathy is certainly multifactorial, in that it is exacerbated by hypermagnesaemia and hypercalcaemia. Nerve function and muscle strength improve following parathyroidectomy. However the most likely explanation is that retention of uremic toxins leads to a reduction in energy dependent processes, and failure to transport and assemble tubulin within the cell correctly. The ouabain sensitive calcium ATPase pump activity has been shown to be decreased in uremia, thereby affecting sodium-calcium exchanger.

Various 'uremic toxins' have been proposed, including guanidine compounds, particularly methylguanidine which can inhibit the sodium ATPase pump, polyamines, phenol metabolites, myoinositol, and 3-Carboxy-4-methyl-5-propyl-2-

fluranpropanoic acid, which inhibit organic acid transport. Other suggestions include toxin induced inhibition of other key enzymes, such as transketolase, and pyridoxal-phosphate kinase. But the nature of the uremic toxins remain obscure[35]. Fraser and Arieff[16] postulated that neurotoxic compounds deplete energy supplies in the axon by inhibiting nerve fiber enzymes required for maintenance of energy production. Although all neuronal perikarya would be affected similarly by the toxic assault, the long axons would be the first to degenerate since the longer the axon, the greater the metabolic load that the perikaryon would bear. In toxic neuropathy, dying back of axons is more severe in the distal aspect of the neuron and may result from metabolic failure of the perikaryon. Energy deprivation within the axon may be especially critical at nodes of Ranvier, since these nodes demand more energy for impulse conduction and axonal transport. It was postulated that membrane dysfunction was occurring at the perineurium, which functioned as a diffusion barrier between interstitial fluid and nerve, or within the endoneurium which acted as a barrier between blood and nerve. As a result, uremic toxins may enter the endoneurial space of either site and cause direct nerve damage and water and electrolyte shifts with expansion or retraction of space.

The Middle Molecule Hypothesis in CRF

It is postulated that uremic neuropathy occurred due to accumulation of a dialyzable substance on the basis of their observational studies that demonstrated improvement in neuropathy in two subjects with long standing CRF following commencement of dialysis therapy. Later studies demonstrated that patients treated with peritoneal dialysis had lower rates of uremic neuropathy despite the fact that these patients frequently had higher blood urea and creatinine concentration[36]. The lower neuropathy rate in the peritoneal dialysis group was thought to indicate that the substance responsible for neuropathy was better dialyzed by the peritoneum than by the cellophane membranes used in hemodialysis. On this basis, the most likely group of substances was thought to be the “middle molecules” substances with a molecular weight of 300-12000 Daltons given that such substances were known to be poorly cleared by hemodialysis membranes.Marked elevations in the concentrations of middle molecules have been demonstrated in CRF patients, a finding not observed in healthy controls. Examples of such molecules include parathyroid hormone (PTH) and B-2 microglobulin, the levels of which are elevated in patients with CRF. Further studies demonstrated that the use of thinner dialysis membranes and longer dialysis times, strategies that would have greater benefits for the clearance of middle molecules compared to small molecules, led to significant reductions in the rate of severe neuropathy. A study using a hemodialysis membrane highly permeable to middle molecules also demonstrated a dramatic reduction in the development of neuropathy[24].There is lack of conclusive evidence that any single molecule in the middle molecular range is actually neurotoxic. In a study of nerve conduction velocity following renal transplantation, correlation was noted between the postoperative concentration of myoinositol, a middle molecule, and median sensory conduction velocity. Although myoinositol levels are elevated in CRF patients, there is little convincing evidence for a neurotoxic effect.The only middle molecule for which some evidence of neurotoxicity exist is PTH, with some studies suggesting a link between PTH and the neurological complications of CRF. PTH has been shown to prolong motor nerve conduction velocities in animal studies, although human studies of the effect of PTH on peripheral nerves have yielded conflicting results, with variable changes in motor nerve conduction velocity in patients with CRF.

Despite the short comings of the middle molecule hypothesis, the hypothesis that a dialyzable toxin may be involved in the pathophysiology of this condition remains prevalent. More recently, it has been suggested that the following criteria should be met in order for a substance to be truly regarded as a uremic neurotoxin:

1. It must be an identifiable chemical;
2. It should be elevated in blood of uremic patients;
3. There should be direct positive relationship between blood level and neurological dysfunction;

4. It should cause neurological dysfunction in animals at appropriate blood levels; and
5. Its removal from the blood should abolish dysfunction.

The middle molecule hypothesis fails to satisfy a number of these criteria, most importantly criteria 3, as there is little evidence to suggest that such molecules are actually neurotoxic.Despite the evidence that a dialyzable toxin may underlie the development of uremic neuropathy the mechanism of this neurotoxicity remain unclear. The possibility that the neurotoxic effect may be due to alteration in membrane excitability was first proposed by Nielsen who, drawing on evidence from in vitro studies of muscles and red blood cells in CRF patients proposed that one or more of these toxins may cause neuropathy by inhibiting activity of axonal Na^+/K^+ pump. This energy dependent pump is electrogenic with three Na^+ ions being pumped out for every two K^+ ions pumped into the axon, leading to net deficit of positive charge on the inner aspect of axonal membrane. Paralysis of the Na^+/K^+ pump abolishes the direct contribution of the hyperpolarizing pump current to the membrane potential and leads to accumulation of extracellular K^+ that causes further depolarization. The Na^+/K^+ pump is therefore of critical importance in maintaining normal ionic gradients, which are essential for axonal survival. Disruption of these gradients may cause reverse operation of the Na^+/Ca^{2+} exchanger, leading to increased levels of intracellular Ca^{2+} and axonal loss.Although it is not possible to measure membrane potential directly in human axon in vivo, indirect information regarding membrane potential and axonal ion function may be gained from nerve excitability studies. Excitability techniques provide information regarding alteration in membrane potential and axonal ion channel function based on coherent changes in a number of different indices. Nerve excitability measures have been used to study peripheral nerves in patients with neuropathy and have provided information about disease pathophysiology.

Neurophysiological Findings in CRF

Early studies of uremic neuropathy utilizing nerve biopsy techniques revealed prominent axonal degeneration, most severe in the distal parts of nerve trunks. Although initial studies suggested that demyelination was a significant feature of uremic neuropathy, subsequent reviews demonstrated that demyelination was secondary to axonal loss and that proximal segments of the nerves were relatively spared[18].These findings supported the concept that uremic neuropathy was a dying back neuropathy, with metabolic failure of the neuron causing distal axonal degeneration. Numerous neurophysiological series have been under taken in patients with uremic neuropathy and have demonstrated findings consistent with a generalized neuropathy of axonal type[13]. Early studies focused on motor nerve conduction parameters and demonstrated slowing of conduction velocity in patients prior to the development of clinical neuropathy. Subsequent studies demonstrated abnormalities of nerve conduction with generalized slowing in both sensory and motor nerves, accompanied by reduction in sensory response amplitudes. Motor response amplitudes tend to remain relatively preserved, although abnormalities in lower-limb motor nerves were noted in some patients, accompanied by neurogenic changes in distal lower-limb muscles on electromyography.An abnormality of sural nerve conduction and/or late response latency was observed in 100% of 30 randomly selected patients with chronic renal failure (18 receiving hemodialysis), although five were without clinical signs or symptoms[38]. This confirms the importance of these studies in the early detection of peripheral nerve disorders in patients with chronic renal failure. Other groups have confirmed similar findings, demonstrating reduction in sensory and motor response amplitudes in addition to abnormalities of late responses[19,39]. Reduction in peroneal nerve motor conduction velocity and prolongation of tibial F-ware minimum latencies have been established as sensitive indicators of neuropathy in CRF patients. Prolongation of soleus H. reflexes has also been demonstrated in patients without clinical evidence of neuropathy, suggesting that this parameter may be more sensitive in detecting early neuropathy. Studies of quantitative sensory testing in CRF patients have demonstrated increased vibratory perception thresholds most marked in the

lower limbs. Somato-sensory evoked potentials in EKSD patients demonstrate abnormalities of conduction along both the distal and proximal segments of peripheral somesthetic pathways, but less commonly along intracranial sensory pathways.A study of single fiber electromyography demonstrated normal fiber densities in motor units of CRF patients[40]. These findings suggested that reinnervation, characterized by increased fiber density, had failed to occur. However, this was accompanied by increased jitter, possibly reflecting peripheral demyelination in the setting of axonal degeneration. A further single-fiber EMG study established that jitter abnormalities improved following a year of dialysis.Early studies of nerve excitability, utilizing a limited range of excitability parameters, demonstrated an elevated threshold for excitation even when nerve conduction values were normal, in addition to demonstrating prolongation of absolute and relative refractory periods[40]. As a consequence, it was concluded that the safety factor for neural transmission at the nodes of Ranvier would be lowered. Unexpectedly, uremic nerves retained vibratory perception and their, sensory response amplitudes for a longer period than control nerves when rendered ischemic. Uremic nerves also behaved differently when temperature was lowered, with a less rapid rise in response amplitude compared to controls.In addition to the slowly progressive sensorymotor axonal neuropathy, a more rapidly progressive motor neuropathy has also been described. A small number of CRF patients with diabetes have also been shown to develop a subacute neuropathy progressing over a few months, with severe muscle weakness. In this group of patients, nerve conduction studies may demonstrate features of either a demyelinating or axonal neuropathy. Although the presence of diabetes complicates assessment of nerve conduction data, the absence of pre existing neuropathic symptoms and the clinical improvement noted following dialysis or transplantation suggest a metabolic basis for the neuropathy related to underlying CRF. Analysis of cerebrospinal fluid (CSF) is rarely helpful, as CSF protein concentration is frequently elevated in CRF patients and may simulate the albumino-cytologic dissociation that is characteristic of Guillain-Barre Syndrome.

Small-fiber neuropathy many develop as a clinical entity in CRF patients. Lindblom and Tegner[25] demonstrated abnormalities of thermal sensation in 30% of CRF patients and concluded that small-fiber neuropathy may exist as a distinct entity in these patients. These results however, differed from those of other groups who demonstrated minimal impairment of thermal sensation in CRF. In a study of 20 CRF patients, abnormalities in standard nerve conduction studies were demonstrated in 16 patients, whereas abnormal thermal threshold were found in only 6 patients and, when present, did not correlate with clinical evidence of polyneuropathy. Such findings are consistent with those of pathological studies that demonstrated greater vulnerability of large-diameter fibers in CRF patients.

Pathophysiology of Nerve Excitability and Conduction Abnormalities

The chief role of the axon is that of impulse conduction, which depend on electrical cable structure and voltage dependent ion channels of the axonal membrane. In the myelinated axons from peripheral nerves, voltage sensitive Na^+ channels are clustered at high densities (upto 1000/μm) in the nodal region, compared to the internodal region (25/μm)[41]. The high density of Na^+ channels at the node reflects the need of saltatory conduction for a large inward current at the node. When nodal membrane is depolarized, an inward current is established, carried by Na^+ ions. The Na^+ conductance is voltage sensitive and regenerative: it increases with depolarization, and this in turn leads to greater depolarization as well as depolarization to the next node. Na^+ channels are membrane-spanning protein molecules, containing a pore unit (a-subunit) through which Na^+ ion can diffuse almost freely in the open state. A variety of toxins and drugs bind to the a-subunit of Na^+ channels. Nerve excitability studies in CRF patients have demonstrated significant alterations in membrane potential prior to haemodialysis, with recovery in the post dialysis period.

Measures of motor and sensory nerve excitability have been assessed in relation to changes in serum

levels of potential neurotoxins including K^+, Ca^{2+}, urea, uric acid and middle molecules such as PTH and B-2M. Predialysis excitability abnormalities were noted to be strongly correlated with serum K^+ in all studies, suggesting that hyperkalamic depolarization may underlie the development of uremic neuropathy. Furthermore, abnormalities of excitability become apparent with serum K^+ concentrations in the high normal range, well below the levels required to produce cardiac toxicity. The excitability abnormalities in CRF patients were also different from those noted in patients with diabetic neuropathy, another common metabolic neuropathy, suggesting that the abnormalities noted in CRF patients were not purely a consequence of structural change. K^+ satisfies criteria that have been suggested for a substance to be accepted as a uremic neurotoxin. It is an identifiable chemical that is elevated in the serum of CRF patients and causes neurological dysfunction in both humans and animals. A direct relationship exists between serum levels of K^+ and neurophysiological parameters, and its removal leads to considerable improvement in these indices[18]. Inhibition of the Na^+/K^+ pump by uremic neurotoxin, previously proposed as the mechanism underlying the development of uremic neuropathy, may induce membrane depolarization. On the other hand alteration in membrane potential and intra and extra cellular K^+ concentration have a direct effect on Na^+/K^+ pump function.

Effects of Dialysis and Transplantation on Neuropathy in CRF

Early reports investigating the effects of hemodialysis on uremic neuropathy suggested that some patients with mild neuropathy recovered completely with adequate dialysis. In fact, failure to improve was considered to be an indicator of insufficient dialysis. These reports, however, did emphasize that the extent of improvement was likely to be related to the severity of neuropathy and that patients with severe neuropathy were unlikely to experience any significant recovery. More recent studies, however, have demonstrated that improvement in neuropathy with dialysis is an uncommon event. Although these studies suggest that dialysis retards the progression of neuropathy in most patients, in some cases a gradual deterioration of neuropathy may occur.A comparison of hemodialysis and peritoneal dialysis with regard to neuropathy progression has demonstrated no significant difference between the two dialysis forms.

Renal transplantation remains the only known cure for uremic neuropathy with clinical improvement in sensory and, to a lesser extent, motor function occurring within a few days of transplantation[10]. Serial nerve conduction studies following transplantation demonstrated a correlation between the improvement in the nerve conduction and biochemical parameters, suggesting that metabolic phenomena may underlie the rapid improvement. Even with severe neuropathy, improvement in symptoms and signs may occur within one month of transplantation, although in some patients the recovery is prolonged or remain incomplete.

Dialysis and transplantation are less beneficial for patients with autonomic neuropathy compared to large-fiber neuropathy. An early study suggested that autonomic function may be improved with dialysis, but a later report failed to show any significant benefit[11]. Although renal transplantation may lead to improvement or normalization of autonomic function,[12] the time course of such improvement is often slow and may be incomplete, with significant change often occurring after 4-8 years[23]. Recent evidence suggests that the treatment with erythropoietin (EPO) may prove beneficial in CRF patients with neuropathy as well as for patients with neuropathy due to other etiologies[42]. Treatment with EPO improved motor nerve conduction velocity in CRF patients, but had no effect on sensory indices. In vitro studies have shown that EPO receptors are present on schwann cells and in dorsal root ganglion neurons[43]. Up regulation of EPO receptors occur after axonal injury, mediated by release of nitric oxide, and administration of exogenous EPO is associated with reduction in limb weakness and neuropathic pain behavior.

Conclusion:

Neuropathy occurs in 60 to 100% patients of ESKD. The first clinical documentation of neuropathy was

provided in the early 1960s. Peripheral neuropathy in end-stage kidney disease presents as a length-dependent, distal sensorymotor symmetrical polyneuropathy with greater lower limb than upper limb involvement. It generally develops at a glomerular filtration rate of less than 12 ml/min. The most frequent clinical features are those of large-fiber involvement, with paresthesias, reduction in deep tendon reflexes, impaired vibration sense, weakness and muscle wasting. Mononeuropathies are also a frequent clinical complication in CRF patients and most typically occur in the median, ulnar, and femoral nerves. In uremia susceptibility of the peripheral nerves to compression and local ischemia is increased. Autonomic neuropathy may develop in CRF patients and can play a role in the pathogenesis of intradialytic and orthostatic hypotension, in incontinence, diarrhoea, constipation, oesophageal dysfunction, hyperhydrosis and impotence. The pathologic features of peripheral neuropathy in patients of CRF are striking axonal degeneration in the most distal nerve trunks with secondary segmental demyelination. The condition has a predilection for large diameter axons, with relative sparing of the unmyelinated and small myelinated afferent neurons. The precise cause of uremic neuropathy remains unknown. One or several neurotoxic molecules of molecular weight 300-12000 Daltons called the “middle molecules” have been implicated in the pathogenesis of neuropathy of CRF. A comparison of hemodialysis and peritoneal dialysis with regard to neuropathy progression has demonstrated no significant difference between two dialysis forms. Renal transplantation remains the only known cure for uremic neuropathy with clinical improvement in sensory and, to a lesser extent, motor function occurring within a few days of transplantation.

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Bangladesh Journal of Neuroscience 2012; Vol. 28 (2) : 128-131

CASE REPORTS

Arsenic Intoxication Presenting as Peripheral Neuropathy

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Abstract:

Chronic Arsenic Toxicity may have varied clinical presentations ranging from non-cancerous manifestations to malignancy of skin and different internal organs. Chronic arsenic exposure results in dermatologic manifestations prior to overt clinical neuropathy. Arsenic neuropathy causes painful paresthesias and, with higher level or continued exposure, length-dependent weakness. We are reporting two cases of chronic arsenic poisoning who presented initially as peripheral sensory motor neuropathy and skin manifestations. Arsenic poisoning was suspected because many of the other family members also developed similar symptoms simultaneously. The hair samples of these patients contained markedly elevated levels of arsenic. Also the water samples from their household and the neighboring households were found to have alarming levels of inorganic arsenic. Provision of arsenic free drinking water halt further deterioration of symptoms and there was significant improvement of their dermatological & neurological conditions.

Keywords: *Arsenic, Arsenicosis, Peripheral Neuropathy*

Introduction:

Arsenic is a metallic compound. Arsenic forms colorless, odorless, crystalline oxides. It is found in trivalent & pentavalent form. Its salts are called arsenates which is the basis of arsenic contamination of groundwater. Trivalent arsenate has greater human toxicity than pentavalent arsenate. It is one of the most potent toxins affecting GI system, neurological, renal, hepatic system, and skin. A significant level of arsenic is found in drinking water in almost all regions of Bangladesh. Reports have demonstrated that there is a large-scale problem in Bangladesh and India due to contamination of the groundwater, causing exposure to become endemic.

In these areas a high proportion of individuals (10 to 20%) examined have evidence of arsenical toxicity. Of those with toxicity, peripheral neuropathy is a common finding. Arsenic toxicity occurs both acute & chronic forms. The clinical manifestations of arsenic exposure depend on the level of exposure. High-dose exposure results in rapid onset of severe gastrointestinal disturbance (e.g., abdominal pain, vomiting, and diarrhea), as well as tachycardia, hypotension, and vasomotor collapse with possible death. In addition, CNS dysfunction may occur, which can be transient (e.g., organic psychosis, somnolence, or stupor) or prolonged (e.g., behavioral and cognitive problem).If the subject survives acute high-level exposure, the neuropathy begins to manifest within weeks and may continue to worsen for a period of weeks after removal from exposure (coasting). Sensory symptoms including painful paresthesias and numbness predominate. Burning, aching, and tingling are positive sensory phenomena that occur first in the toes and feet, but later in the fingers. Similarly, weakness follows a length-dependent pattern, starting with the feet and later involving the hands. With high-dose exposure or inadequate treatment, the weakness may progress to involve the respiratory muscles and mimic Guillain-Barré syndrome. The deep tendon reflexes are depressed or absent early in the process. Other neurological

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manifestations include headache, visual disturbances & features of encephalopathy in acute arsenic intoxication.

Chronic arsenicosis are highly variable and depend on the levels and duration of arsenic exposure as well as the degree of host susceptibility. One of the early warning signs of arsenic poisoning is a "pins and needles" sensation in hands and feet. Clinical neuropathy characterized by burning and numbness of the feet and later the hands results from continued exposure. This involves both small and large fiber sensory disturbance with resultant difficulties with proprioception, in addition to the dysesthesias. Weakness tends to be mild and limited to the most distal muscles. Recovery is related to the severity of the neuropathy at the onset of treatment. Mild cases recover completely, whereas more serve cases may have significant residua.

Case Report:

A 26-year-old farmer, normotensive , non-diabetic, right handed person hailing from Kishoregonj ,admitted in Bangabondhu Sheikh Mujib Medical University, Dhaka with the complaints of burning sensation of hands & feet for 2 months & progressive weakness of both upper & lower limbs for 20 days. He also complaints of blackish discoloration of skin all over the body more marked in the palms & soles. All other 5 family members (excluding one of his brother who lived in Chittagong) also develop hyperpigmentation of palms and soles, and tingling, numbness along with this patient. The patient and his family members gave a history of water consumption for drinking and cooking from deep bore well (using a submersible pump) for last 6 months. Before this they had used water from another arsenic free labeled deep tube well. No bladder-bowel involvement was present. Examination revealed hyperpigmentation of face, arms, legs, upper chest, and abdomen,palms and soles. Sensory motor symmetrical predominantly distal, peripheral neuropathy was present with muscle power around 4/5 in all 4 limbs, all jerks are absent. All modalities of sensation are impaired.

We also examined one of his brother & got similar findings.Electrophysiologically, severe axonopathy was present. The arsenic level was significantly high in hair sample of both of them (33.95mg/kg, & 46.60mg/kg respectively, normal level <3.0mg/kg by atomic absorption spectrometry).Water sample of deep bore well was sent for arsenic estimation where arsenic level was found 3.53mg/l(standard limit .05 mg/l) .

Biochemical tests and haemogram , hormone profile(TSH 2.77IU/ml, ACTH 24.0pg/ml, cortisol 454nmol/l,) were normal .Treatment for arsenic poisoning for this patient and all his family members was started with oral D- penicillamine.The water source has since been changed from deep bore well to government supply arsenic free deep tube well water. After two months follow up, skin lesion had subsided in this patient as well as in all of his family members. There was mild relief from symptoms of peripheral neuropathy after two months of treatment, but complete recovery from symptoms of peripheral neuropathy has not yet occurred.

Discussion:

Peripheral neuropathy, hyperpigmentation, hyperkeratosis, exfoliative dermatitis, are the features of sub-acute or chronic arsenic intoxication[1]. Peripheral neuropathy[2] which occurs in chronic arsenic poisoning may manifest between 1 - 2 weeks after recovery from acute poisoning and is in the form of both demyelinating and distal axonopathy[1]. The symptoms of encephalopathy (headache, drowsiness, mental confusion, delirium) may also occur as part of chronic intoxication.

Arsenic exerts its toxic effect by reacting with sulphydril radicals of certain enzymes necessary for cellular metabolism. Inorganic arsenic is readily absorbed (lung and GI), sequestered in liver, spleen and kidneys. Residues persist in skin, hair, and nails for a long time. The diagnosis of arsenic poisoning depends upon the demonstration of increased level of arsenic in hair and urine[3]. Arsenic is deposited in the hair within 2 weeks of exposure and may remain fixed there for long periods. Concentration of >0.1 mg arsenic per 100 mg hair are indicative of poisoning.

Arsenic also remains within bones for long periods and is slowly excreted in the urine and faeces[3]. WHO Guidelines for drinking water published in 1999 suggested that arsenic concentration should be < 0.01 mg/litre (< 10 microgram/l.) and more than 50 microgram/l. is associated with manifestations of arsenic toxicity[4].Excretion of more than 0.1 mg arsenic per liter of urine is considered abnormal (no sea foods should have been consumed for 24 hours before collection of specimen)[5].Individuals who consume fish on regular basis, as occurs in coastal regions may have slightly or moderately elevated level of arsenic.

In our case, arsenic poisoning manifested by symptoms of peripheral sensory motor neuropathy in the form of abnormal sensations (tingling, numbness and decreased sensation), and dermatological manifestations (hyperpigmentation of palm and sole). Skin manifestations in our patient are similar to those described by Saha *et al*[6] in which arsenic in tube-well water is associated with hyperpigmentation.

Peripheral neuropathy[2] is the main feature of subacute or chronic organic poisoning and is the predominant symptom in our patient as described in literature including Hafeman *et al*[7]. Similar neuropathy due to arsenic toxicity is also described by Chuttani[1]. The possible cause of arsenic poisoning in our patient is arsenic present in deep bore well water. Symptoms of arsenic intoxication only occurred in our patient after starting of consumption of water from deep bore-well. Study conducted in Taiwan[8] showed that subjects who drank well water containing arsenic concentration > 50 microgram/l. have peripheral neuropathy evidenced by slow conduction velocity on Nerve conduction study.

Recommended treatment for acute arsenic poisoning consists of gastric lavage, vasopressor agents, fluid and electrolyte maintenance, and BAL(British anti lewisite)[9]. Maintenance of renal perfusion and exchange transfusion is required if massive haemoglobiuria occurs as in chronic poisoning. Oral succimer (DMSA & D-penicillamine[10]) vitamin supplement are also required. After change of their water source and treatment with oral D-penicillamine and supportive care, skin lesions resolved but complete recovery from peripheral neuropathy did not occur. Sensory neuropathy predominates over motor as described by Rehman *et al*[11]. Similar type of neuropathy was detected in our patients.

Conclusion:

Arsenic toxicity is a problem in Bangladesh due to contamination of ground water & many people are suffering from Arsenicosis. They manifest as different skin, GI, cardiac ,respiratory & neurological problems. These problems mostly occur due to chronic exposure to Arsenic. Neurological manifestation may be asymptomatic asymptomatic or may present with sign symptom of peripheral neuropathy. Neurophysiological evaluation may help to diagnose these cases. So early diagnosis, prevention of arsenic exposure & appropriate treatment can reduce the sign symptoms of peripheral neuropathy but complete cure can not be attained.

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Bangladesh Journal of Neuroscience 2012; Vol. 28 (2) : 132-140

A Case of Idiopathic Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Abstract:

A 40 years old man presented with progressive weakness and distal paraesthesia of limbs with difficulty in walking for last seven years. As the patient was not investigated thoroughly, a diagnostic dilemma was persisted. This patient went abroad & investigated thoroughly and yet not reached to a confirm diagnosis. Subsequently this patient reported to us and diagnosed it to be a case of Idiopathic Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) responded to oral steroid therapy. After follow-up, this patient showed marked improvement. So diagnostic dilemma that persisted with such a patient that showed improvement with treatment and a challenge to a treatable condition had encouraged us to report the case.

Keyword: *Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Idiopathic, Steroid.*

Introduction:

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a clinically heterogeneous, grossly symmetric, sensory and motor neuropathy evolving as a monophasic, relapsing, or progressive disorder. It develops over more than 8 weeks, distinguishing the condition from Guillain-Barre syndrome (GBS), which has an acute onset.

CIDP is thought to have an immune basis, its hallmark being inflammatory-mediated demyelination[1]. According to Burns[2], Eichhorst described the first case of chronic and recurrent polyneuritis in 1890, and a few similar cases were reported during the following decades. During the 1950s, the concept of steroid-responsive chronic or relapsing polyneuritis emerged[3]. Along with experimental studies, this notion pointed to an immune mechanism. Later, investigators showed that reduced conduction velocities and conduction block resulted from segmental demyelination, which was considered typical findings of CIDP and related disorders[4].For years, various terms were used to describe the condition and in 1982, Dyck and coworkers[5] used the term chronic inflammatory demyelinating polyradiculoneuropathy, which summarizes its clinic pathological features.

Clinical trials have subsequently proven the efficacy of immunotherapy in patients with CIDP, and, to aid recognition of these patients, the American Academy of Neurology (AAN) proposed research diagnostic criteria[6].During the following years these criteria seemed insufficiently sensitive for clinical practice, so new sets were proposed by several experts[7].In 2008, the French CIDP Study Group provided recommendations on diagnostic strategies for typical and atypical cases to help to improve diagnosis of this neuropathy[8].

Although most patients with CIDP are recognized, since we still do not have definitive diagnostic tests, diagnosis can sometimes be challenging. Moreover, the prevalence of CIDP, which varies roughly between one and seven in 100 000 across studies, is probably underestimated, partly because of an absence of recognition of possible or probable cases[9]. In view of its clinical variability, the

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diagnosis of CIDP should be envisaged during investigation of almost any multifocal or generalized neuropathy of unknown cause. This consideration is important because the condition is treatable[10]. Diagnosis is sometimes challenging and can require use of imaging and nerve biopsy. Raised protein concentrations in CSF and heterogeneous slowing of nerve conduction are typical of the condition. Steroids and intravenous immunoglobulin are effective, and plasma exchange can be helpful as rescue therapy. The usefulness of immunosuppressants needs to be established. The identification of specific diagnostic markers and new therapeutic strategies with conventional or targeted immunotherapy are needed to improve the outlook for patients with CIDP. Recent advances have been made in CIDP and other immune-mediated neuropathies.

Herein, we present a case of CIDP-I in a middle aged man presented with progressive weakness, paresthesia & numbness of all limbs with significant impairment of walking for last seven years and no systemic complaints and that was diagnosed with clinical findings and specific investigation and typed by literature review.

Case Report

A 40 years old Bangladeshi Bengali man admitted in Bangabandu Sheikh Mujib Medical University Hospital with complains of gradually increasing weakness of all the limbs for last 7 years. Initially weakness started in right hand and after few months the left hand was affected. Then the both lower limbs were affected. The weakness was gradually increasing as he had difficulty in holding objects and also had difficulty in walking. These symptoms were associated with wasting of the muscles. He also complaints of tingling and numbness of both hands and feet without bladder bowel involvement.

He was non-smoker, non-alcoholic, non-diabetic and non-hypertensive and hailing from non-arsenic prone area. He was married without promiscuity of any kind & no one of his family member was suffering from similar disease. He had no occupational exposure to environmental toxin and on average Bangladeshi food. He had no joint pain or any systemic diseases.

Examination of the patient revealed that he was of average build with Pulse 80/min. B.P 130/80 mmHg & mild bilateral non tender lymphadenopathy of both axilla measuring 2 cm × 1.5 cm was found. He was not anemic and clubbing of the fingers, edema of legs and jaundice were absent and featureless abdomen without any organomegaly. Neurological examination revealed that higher psychic function was normal. Speech was normal. All the cranial nerves on both sides were normal. Motor system examination revealed wasting of muscles of hand & feet on both side and tone was mildly reduced. Muscle power was Grade-4. All the deep tendon reflexes were diminished but the ankle jarks on the right side was absent.Babinski signs were absent There was foot drop on right side. His gait was stamping with foot drop on right side. Sensory function showed that there was 45% of hypoaesthesia and reduced pain sensation in the both hands and feet. Romberg's test was negative. No other neurological abnormality was found including no enlarged palpable nerve.

Investigation of the patient showed Hb % was 80%, ESR-75mm in 1st hour, differential count of WBC (N- 59%, L-28%,M-6%,E-5%, B-2%) and morphology HCT-37.5%, MCV-83.6fl, MCH-25.9pg, MCHC-310g/L and Platelet- 301×10/L. RBS-6.36mmol/L. Serum urea, creatinine & electrolyte were within normal limit. Serum bilirubin -6. 6 µmol/L, Total protiem-69. 8 g/L, S. Albumin - 35gm/L, S. Globulin - 34. 8gm/L, AlK. Phosphatase-100unit/L, Alanine Aminotrasferase-32unit/L, Aspartate Aminotrasferase-14unit/L, γ-glutamyl trasferase-67 unit/L, Lactate dehydrogenase- 146 unit/L, Creatinine kinase- 82unit/ L, P.T.-9.4 sec. APTT-24.8sec.Routine urine & stool examination was normal. Rh. Factor was negative. C. Reactive protein-10 mg/L. Double stranded DNA and Anti-nuclear antibody was negative. Serum c- ANCA was positive in 1:40 dilution. Serum HBsAg (-) negative. HIV antibody (-) negative. Serum protein electrophoresis showed Albumin -38.8%, α-globulin-17. 5%, β-globulin-11.8,-globulin-24.9%. S. Folate- 3.2ng/ml, Vit. B12-456pg/ml. S. Amylase-36unit/L, S. Lead-0. 70 /L, S. Cu.-18. 6 mol / L, S.

Zn.-12 mmol/L. FT3-5. 36 pmol/L. FT4-23.13pmol/L. TSH-2. 80mIU/L. S.Ca.-2.23mmol/L. S. Inorganig phosphatase-0.93mmol/L. S.Magnesium-0.79mmol/L. USG of abdomen was normal. C.T. Scan of brain was normal. Abdominal aortogram & selective bilateral renal angiography showed no sign of vascularity or microaneurysm was found. Histopathology of left axillary lymph node showed reactive changes without evidence of malignancy & Reed-Sternberg cells. Bone marrow examination was normal and storage of iron is normal. CSF was clear, CSF protein 65 mg/dl, CSF WBC- nil, RBC- 80/ mm^3& Gram Staining showed no organism & C/S was negative. CSF culture for AFB & virus was negative and both CSF & blood electrophoresis revealed no oligoclonal band. Right Sural nerve biopsy showed several nerve bundles along with several medium sized blood vessels in the epineurium. There is no evidence of interstitial or perivascular inflammatory infiltrates or abnormal deposits. Special stain for myelin showed moderate to severe loss of myelinated fibers with relative axonal preservation.Findings NCS of crossed limbs showed in Table -1

Table-I

Motor nerve conduction

Median nerve , Right Stimulus site	Lat 1 (ms)	Lat 2 (ms)	F wave latency (ms)	Duration (ms)	Amp (mV)	Area	NCV (m/s)
Wrist	2.8	7	4.1	4.2	1.4	3.2	48
Elbow	7.8	11.7		3.9	1.2	2.5	
Ulnar nerve , Right							
Wrist	2.5	7.2	2.6	4.7	1	2.8	55.3
Elbow	7.2	13.4		6.2	1.2	3.6	
Peroneal nerve, Left	Amp (µV)						
Ankle	3.9	8		4.1	90	208	40.5
Fibular head	11.8	16.6		4.8	151	444	

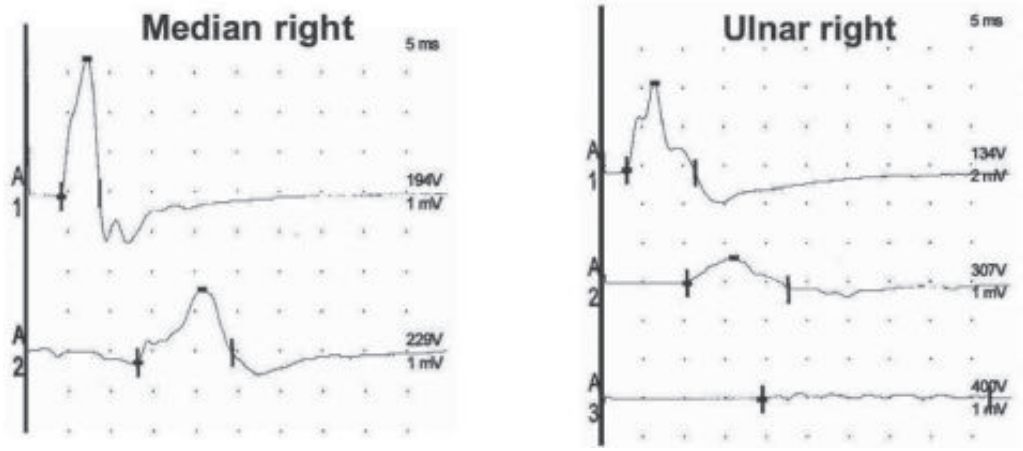

Fig.-1: *Nerve conduction study before treatment illustrating a conduction block on the right ulnar and temporal dispersion on the median nerves.*

Electrophysiological findings were suggestive of chronic inflammatory demyelinating polyradiculo-neuropathy (Table 1 & Fig. 1).

Patient was treated with oral prednisolone 60 mg once a day showed moderate improvement after one month as he can hold objects and walk without assistance and also there was improvement of sensory symptoms. Patient was be followed-up in neurology outpatients department after 3 months and electrophysiological study was carried out which showed improvement from previous study & slow tapering of steroid was done subsequently.

Discussion:

CIDP is relatively uncommon, with prevalence between one in 100 000 in southeast UK[11] and 7.7 in 100 000 in northern Norway[12]. In all studies, CIDP was observed to be most frequent in adult men, as was reported in a Japanese population with an annual incidence of 0.48 per 100 000[13]. CIDP is regarded as an autoimmune disease involving cellular and humoral immunity. However, by contrast with GBS, a single triggering antigen has not yet been found, except in rare cases of CIDP associated with melanoma, in which tumour cells share carbohydrate epitopes with Schwann cells[14].

After the first description by Dyck and co-workers[1], the clinical pattern of CIDP was defined by several features: (i) selective involvement of the peripheral nervous system; (ii) involvement of proximal as well as distal limb structures; (iii) involvement of both motor and sensory fibers (although in some cases motor or sensory fibers only might be affected); and (iv) a recurrent, continuously worsening, or fluctuating course. The classic pattern of limb involvement in CIDP is then a sensory and motor diffuse polyneuropathy with generalized areflexia, and proximal involvement evolving over more than 2 months[6].Cranial nerves are occasionally affected, with a particular tropism for the VIIth pair, but ophthalmoplegia or bulbar weakness can be present[15].The disease course is usually separated into monophasic, progressive, and relapsing forms, although a strict definition of the relapsing form has seldom been used in the literature.

Several variants have been described on the basis of distribution of symptoms and signs16.Although controversies have emerged as to whether some of these syndromes are distinct clinical entities[17].The common pathogenic mechanism of inflammatory demyelination clearly shows that they belong to the spectrum of CIDP[18].Moreover, identification of patients with these variants is crucial because they respond to immunomodulatory therapy as well as patients with the classic phenotype.

CIDP can be associated with various conditions, including hepatitis C, inflammatory bowel disease, and lymphoma, monoclonal gammopathy of undetermined significance (MGUS), HIV/AIDS infection, organ transplant, and connective tissue disorders. Similarly, investigators have reported that CIDP was more frequent in patients with diabetes mellitus than it was in the general population[19], although this assumption has been challenged[20].Several reports have shown subclinical involvement of the central pathways in some patients, suggesting that CIDP might involve the central as well as the peripheral nervous system[21]. This finding seems to differ from that of a population of patients in whom there is an association between a CIDP-like disorder and a multiple sclerosis-like condition, in which clinical involvement of the peripheral as well as the central nervous system is obvious[22]. Finally, CIDP has been reported in patients with Charcot-Marie-Tooth disease[23], suggesting that superimposed inflammatory mechanisms might occur in hereditary neuropathies and contribute to disability[24].

Childhood CIDP has been extensively reported, allowing a precise picture to be drawn of the presentation, response to treatment, and prognosis[25]. Overall, children with CIDP have a more rapid onset, greater disability at the peak of the disease, and a more frequent relapsing course than do adults, but respond better to treatment and have a more favourable long-term outcome.

Nerve conduction findings are a key part of diagnostic investigation for patients with suspected CIDP. Indeed, slowing of nerve conduction mainly occurs during nerve demyelination, either diffuse or segmental, and is highly suggestive of CIDP in

the appropriate clinical situation[1]. Following the work of Albers and Kelly, 85 consensus electrophysiological research criteria for CIDP were elaborated in the early 1990s[6]. Several variables were considered: (i) slowing of motor nerve conduction velocities; (ii) lengthening of distal motor latencies; (iii) prolonged minimal F wave latencies; and (iv) partial conduction block. The severity of slowing in individual nerves and the number of nerves in which abnormalities had to be found were carefully chosen to be specific enough for research purposes, but several investigators have judged the sensitivity of these criteria to be insufficient for clinical practice.Therefore, several sets of electrophysiological criteria for CIDP have been proposed to improve detection of patients with this treatable disorder[7]. Thaisetthawatkul and colleagues[26] showed that dispersion of distal motor action potentials was another useful criterion, and others, including a panel of experts from the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS), have proposed that this measure be included in electrophysiological criteria for CIDP[27].The EFNS/PNS criteria seem to provide the best chance of identification of patients with CIDP and whether axonal forms of CIDP exist has been a matter of debate. Axonal involvement in this primary demyelinating neuropathy is obvious in many cases and is closely linked to disability. Uncini and co-workers[28] described five patients with a condition they called steroid-responsive axonal polyneuropathy, suggesting that it was an axonal variant of CIDP.However, whether the inflammatory process directly involves axons, the condition being the chronic counterpart of acute motor sensory axonal neuropathy, is far from proven from this study. Indeed, patients who do not meet neurophysiological criteria for a primary demyelinating neuropathy might have evidence of inflammatory demyelination on nerve biopsy[2].

Many patients with CIDP have raised CSF protein with leukocyte counts lower than 10 WBC per ìL, which is indicative of root inflammation, and this disease criterion was in the past regarded as mandatory[1]. However, as has long been recognized, protein content can be normal in at least 10% of patients, and the criterion is now considered supportive[6]. When leukocyte count is raised in the CSF, Lyme borreliosis, HIV/AIDS infection, lymphoma, or sarcoidosis should be considered. Since root involvement is not accessible to conventional nerve conduction studies, somatosensory evoked potentials have been investigated in patients with chronic demyelinating neuropathies[29]. This technique might be especially useful when assessing for proximal involvement of sensory nerves in patients with normal sural sensory potentials. Similarly, breakdown of the blood–nerve barrier at the root level could cause contrast enhancement on MRI[30].Moreover, root hypertrophy can be shown by MRI at the lumbar or cervical level in patients with CIDP and can occasionally cause clinical findings that are attributable to lumbar or cervical stenosis[30]. Because inflammation can be widespread along nerves in CIDP, contrast enhancement and hypertrophy are sometimes shown by conventional MRI at the plexus level[31]. Besides conventional MRI sequences, diffusion neurography, which is a modified diffusion-weighted MRI technique, might be a promising method to identify abnormalities in nerves of patients with CIDP.CIDP mainly affects large myelinated fibers, small fibers are not unaffected, as shown by nerve and skin biopsy findings[32]. The chronic proximal demyelinating lesions frequently induce distal axon degeneration with dropout of large myelinated fibers. On paraffin sections, mononuclear cell infiltrates can be seen as scattered cells, often surrounding vessels. These infiltrates can be seen in the endoneurium, as well as in the perineurium and the epineurium by optic microscopy, but are sometimes more clearly seen by ultrastructural examination. However, the presence of these small clusters of inflammatory cells is uncommon in nerve biopsy samples from patients with CIDP and is not mandatory for the diagnosis. Demyelination and remyelination are pathological hallmarks of CIDP. Segmental demyelination is best seen on teased fiber preparations. The value of nerve biopsy in diagnosis of patients with supposed CIDP has been debated. However, most agree that biopsy should be done

in patients with atypical clinical or neurophysiological findings, and could be considered in patients with poor response to treatment to rule out alternative diagnoses.

CIDP can be associated with some general disorders (paraproteinaemia, diabetes, thyroid dysfunction, neoplasm), probably as a result of a dysimmune process[33],but the association with MGUS is the most common. Indeed, some patients with CIDP have a concomitant IgG MGUS. There is no evidence from published work and our personal experience that these patients should be considered and treated differently from those without monoclonal gammopathy[33]. In some cases of malignant gammopathies, a direct link to the neuropathy needs to be eliminated by nerve biopsy because the monoclonal component or malignant cells can sometimes infiltrate the nervous parenchyma. If the monoclonal paraprotein is an IgM, the distinction between an anti-myelin associated glycoprotein (MAG) neuropathy and CIDP is based on an anti-MAG assay. Most patients with anti-MAG neuropathy are of middle or old age and have a pure sensory ataxic or painful neuropathy, with nerve conduction studies usually showing a disproportionate lengthening of terminal latencies and a severe decrease in motor and sensory responses in the lower limbs.Although CIDP and anti-MAG neuropathy are regarded as distinct entities, there might be some overlap at the clinical, neurophysiological, and neuropathological levels; response to immunotherapy, however, is usually poor in patients with anti-MAG neuropathy. Diagnosis of the multifocal form of CIDP can be challenging, and misdiagnosis with multiple entrapment neuropathy or multifocal motor neuropathy with conduction block is common because of the frequent upper-limb predominance of the three conditions. Similarly, conduction block because of partial nerve ischaemia might erroneously suggest segmental demyelination in patients with multiple mononeuropathy due to necrotizing vasculitis[34].Another challenging issue is the polyneuropathy of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes), which is very similar to CIDP[34]. It does not usually respond to conventional immunotherapy, but rather necessitates radiation therapy for solitary lesions or high-dose chemotherapy.Since the polyneuropathy of POEMS syndrome is usually rapidly disabling, its diagnosis can be a matter of urgency. Nerve biopsy can show specific lesions[36], but the presence of a lambda light chain along with sclerotic bone lesions is usually sufficient to make the diagnosis. Moreover, high serum concentrations of vascular endothelial growth factor are a very useful and specific diagnostic measure for this condition[36]. At any age, but chiefly if patients have a predominantly distal weakness or poor response to treatment, a hereditary neuropathy such as Refsum's disease, Charcot-Marie- Tooth disease, or transthyretin amyloid neuropathy[37] should be ruled out. Finally, the first diagnosis in some patients with CIDP will be chronic idiopathic axonal neuropathy or cryptogenic sensory polyneuropathy, and the disease will be allowed to progress without intervention despite the availability of effective therapy. After some time, any chronic demyelinating neuropathy will induce axonal loss. Patients who do not meet electrodiagnostic criteria for CIDP might benefit from extensive tests including nerve biopsy to look for possible CIDP, especially young patients and those with an aggressive course or prominent motor involvement, since they could benefit from immunotherapy[2].

Steroids have been widely used in CIDP since a single randomized controlled trial showed the efficacy of prednisone[6]. Since then, the usefulness of steroids in CIDP has been confirmed and a controlled study showed that a 6-week course of 60 mg daily oral prednisolone with rapid tapering is as effective as one course of IVIg at 2g/kg[7]. Therefore, recent consensus guidelines concluded that "a trial of steroids should be considered in all patients with CIDP and significant disability"[9].Continuous oral steroid therapy is the commonest regimen used, but some have proposed pulsed high-dose treatment with dexamethasone[45] or oral methylprednisolone[46].Steroid treatment seems to be beneficial in 60–70% of patients with CIDP[47], and long-term treatment needs to be individually tailored according to disease course, with careful attention paid to potential side-effects.

Choice of treatment will depend on several variables, and in particular initial disease severity, age, general health status, and potential contraindications to steroids or IVIg Around 15–30% of patients will not relapse after this first course[8], and for patients who need additional treatment, dose and intervals between courses should be individually tailored to achieve the most cost-effective regimen. If a patient does not respond to one of these first-line therapies, switching to the other is advisable. PE or a combination of steroids and IVIg can be started if neither of these treatments proves effective. Refractory cases might need intensive immunosuppression, as has been proposed by some investigators[47].Long-term maintenance therapy will require careful attention because of side-effects of treatments on the one hand, and because of the risk of relapse and axonal loss on the other.

Available data suggest that the long-term prognosis of CIDP is highly dependent on age at onset, clinical form of the disease, and initial response to treatment. Young patients with a rapid (subacute) onset or a monophasic course are more likely to respond to treatment and recover completely[48].The effect of age of onset seems especially important in elderly people, for whom full recovery after treatment is less frequent than for juvenile patients or adults aged younger than 64 years[49]. Among the clinical variables, proximal weakness has been linked to a higher remission rate and better prognosis compared with the distal phenotype[48].Overall, studies suggest that long-term outcome is usually good in patients with CIDP, especially in those with a monophasic or relapsing course[48].

Conclusions:

CIDP is a potentially disabling immune-mediated neuropathy. Its diagnosis is important because the condition is responsive to several disease-modifying therapies such as steroids, IVIg, PE, and immunosuppressants. In view of recent studies suggesting that prevalence of CIDP has been largely underestimated, we think investigation in a patient suspected of having CIDP should use all available methods, including nerve biopsy. The strategy for diagnosis of CIDP has been reviewed elsewhere[12] and should chiefly be based on clinical presentation and electrodiagnostic evaluation. Ultimately, a trial of steroids or IVIg seems reasonable if sufficient evidence suggests the diagnosis is at least probable. Future research is needed to identify disease markers to improve diagnosis and to develop new therapeutic strategies based on available and emerging therapies.

Conflict of Interest: None

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