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ORIGINAL ARTICLES

Association of Hyperhomocystienemia with Ischemic Stroke

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Abstract:

Background: *Despite conflicting results from prospective studies, substantial evidence is accumulating suggesting that hyperhomocysteinemia may be a risk factor for ischemic stroke.* ***Objective:*** *Our aim was to find out the association of hyperhomocysteinemia with ischemic stroke.* ***Methods:*** *This was a retrospective, case - control study done in the Neurology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU) on 120 subjects with equal number of cases and controls with their age ranging from 15 to70 years.* ***Results:*** *The analysis revealed that homocystiene levels were significantly high in patients with Ischemic stroke compared to controls (15.64±7.58 μmol/L in cases and 11.49±3.99 μmol/L in control group with unadjusted Odd ratio 3.52 (95% CI 1.35-9.35.). Significantly high levels were seen in both male patients compared to controls (16.23±7.58 μmol/L vs. 12.12±3.76 μmol/L and P<0.05) and female patients compared to controls (15.16±9.02 vs. 10.77±4.19 and P<0.05). The homocystiene levels were significantly high in patients with hypertension compared to normotensive patients (16.62±6.6 μmol /L and 9.34±4.11 μmol/L* and *P = 0.01) and in smokers compared to nonsmokers (16.56±6.08 μmol/L and 7.60±2.0μmol/L and P=0.01).* ***Conclusion:*** *Hyperhomocysteinemia is an important independent risk factor for ischemic stroke.* A strong positive correlation was also observed between hypertension, smoking, and high homocysteine levels in the present study.

Key Words: *Hyperhomocysteinemia, Ischemic stroke.*

Introduction:

Stroke is a clinical syndrome characterized by rapid onset of focal or global neurological signs or disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin, non-epileptic and non-traumatic in nature[1]. This definition includes stroke from both infarction and hemorrhage. Transient ischemic attack (TIA) is identical to that of stroke, except

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that the symptoms last less than 24 hours. About 85% of stroke is caused by primary cerebral ischemia resulting in infarction (ischemic stroke) and 15% are caused by cerebral hemorrhage (hemorrhagic stroke)[2,3].

Worldwide, stroke is the leading cause of healthy years lost in late adulthood, and evidence indicates that the burden of stroke, particularly in terms of morbidity and disability, will almost certainly increase in the foreseeable future[4]. Each year, about 4.4 million people die of cerebrovascular disease globally , of whom almost three million are from developing countries[5].

Many risk factors are associated with stroke. So far identified the non-modifiable risk factors are age, sex, race, and ethnicity and the modifiable risk factors include hypertension , diabetes mellitus , smoking, hyperlipidemia , various cardiac conditions, excess alcohol consumption, oral contraceptive use etc[6-8].

Recently there has been much interest in homocysteine (tHcy), a sulfur containing aminoacid as an important risk factor for vascular diseases including stroke, independent of the long-recognized factors like hyperlipidemia, hypertension, diabetes mellitus, and smoking[9].

More than 20 cross-sectional and 3 prospective studies in young and middle-aged and elderly subjects have shown that high levels of homocysteine are associated with an increased risk of myocardial infarction and stroke. These associations were weak or absent in two other prospective studies. However, most prospective studies observed weaker associations with increasing age[10].

The precise mechanisms underlying the apparent adverse effect of hyperhomocysteinemia on the risk of ischemic stroke are not clear at present, although several possibilities can be proposed. Hyperhomocysteinemia may cause a rise in arterial blood pressure thereby increasing the risk of ischemic stroke[11].

Elevated total homocysteine induces oxidative injury to vascular endothelial cells and impairs the production of nitric oxide, a strong vascular relaxing factor from the endothelium[12]. Hyperhomocysteinemia also enhances platelet adhesion to endothelial cells, promotes growth of vascular smooth muscle cells, and is associated with higher levels of prothrombotic factors such as ß-thromboglobulin, tissue plasminogen activator, and factor VIIc[13].

Several prospective studies of white subjects showed a significant association between homocysteine and the risk of ischemic strokes[14], whereas others showed no association[15].

The excess risk of ischemic stroke associated with moderately elevated homocysteine levels did not vary significantly with age or smoking status but was primarily observed among men and non-hypertensive subjects. Several previous studies showed the stronger association of homocysteine with carotid atherosclerosis [16] and stroke risk [17] among non-hypertensive subjects than among hypertensive subjects. It is possible that the risk of ischemic stroke associated with hyperhomocysteinemia may be masked by the presence of hypertension, as hypertension is the predominant risk factor

for stroke. This highly prevalent, potential and emerging risk factor should be addressed and more research is needed to establish hyperhomocysteinemia as a risk factor for ischemic stroke.

Materials and Methods:

Study population:

This was an observational, retrospective, case control study done in the Department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka. Study population was patient of 15 to 70 years of age with WHO defined stroke, ischemic in type, confirmed by CT scan of head/MRI of brain after 4 weeks of attack. Age and sex matched apparently healthy person never suffering from any TIA or stroke events were considered as control.

Statistical analysis:

All data were recorded systematically in preformed data collection form. Unpaired 't' tests were used to compare group means and Chi square test , Odds ratio with 95% confidence interval were done to evaluate differences between groups for other variable. Risk factors analysis was performed by computer based software Statistical Package for social Science (SPSS for windows version 16.0). Probability value <0.05 was considered as minimum level of significance.

Observation and Results:

A total 120 subjects were studied. Of them 60 were ischemic stroke patients and 60 were normal healthy individuals. In this study the age range was15 to70 years with mean (±SD) 49.5±11.8 in case and 50.1±11.6 in control group. (Figure-I)

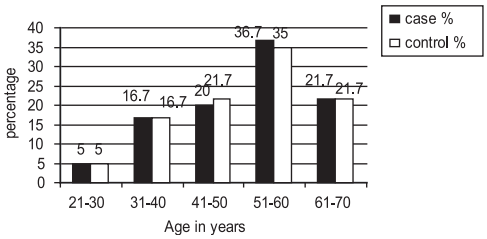

Fig.-1: *Bar diagram showing distribution of age in case and control groups (n-120)*

Male and female ratio in ischemic stroke was 1:0.8 while it was 1:0.87 in the control group(55% vs 45% in stroke group and 53.3% vs 46.7% in control group) (Fig.-2) .

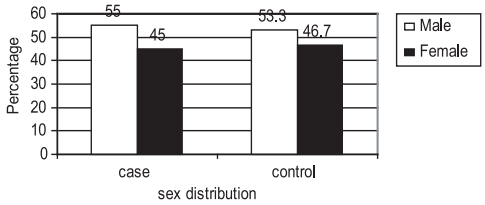

Fig.-2: *Bar diagram showing sex distribution of the study subjects by group (n-120).*

Most of the patients came from low socioeconomic class, which accounted for 45.0% of cases followed by middle and upper class [36.7% and 18.3% respectively] (Fig.-3).

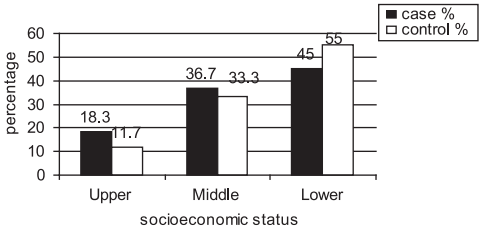

Fig-3: *Bar diagram showing socioeconomic status among case and control groups (n-120)*

The patients were selected as upper, middle and lower class on the basis of monthly income[18].

Upper class- > Tk. 10,000/month
Middle class- > Tk. 5,000 – 10,000/month
Lower class- Tk. 1,000 – 5,000/month

Out of all patients abnormal serum homocysteine level was found 38.3% in case group and 15.0% in control group. The mean (±SD) serum homocysteine level was found 15.64±7.58 μmol/L in cases and 11.49±3.99 μmol/L in control group. Odds ratio 3.52 (95% confidence interval 1.35-9.35). (Table-I)

Out of all patients of present series 20% had diabetes mellitus among the cases with unadjusted odd ratio of 4.75 (95% confidence interval 1.15-22.64, p<0.05) and 51.7%% of patients were hypertensive with unadjusted odds ratio 3.86 (95% confidence interval 1.63-9.30).(Table-II)

Table I

Mean Distribution of Serum homocysteine level (μmol/L) among study subjects (n=120).

Serum homocysteine	Case (n=60)		Control (n=60)		P
level (μmol/L)	No.	%	No.	%	value*
Abnormal	23	38.3	9	15.0	0.001*
Normal	37	61.7	51	85.0	
Mean±SD	15.64	±7.58	11.49	±3.99	

*= significant.

P value reached from unpaired 't' test.

Odd ratio (95% confidence interval) = 3.52 (1.35-9.35).

Table II

Medical history of the study subjects (n=120).

Medical history	Case (n=60)		Control (n=60)		P
	No.	%	No.	%	value
Diabetes mellitus					
Present	12	20.0	3	5.0	0.012S
Absent	48	80.0	57	95.0	
Hypertension					
Present	31	51.7	13	21.7	0.001S
Absent	29	48.3	47	78.3	
Ischemic heart disease					
Present	9	15.0	2	3.3	0.026S
Absent	51	85.0	58	96.7	
Dyslipidemia					
Present	17	28.3	5	8.3	0.004S
Absent	43	71.7	55	91.7	

S= significant

P value reached from chi-square test

Diabetes mellitus: Odds ratio (95% confidence interval) = 4.75 (1.15-22.64)

Hypertension: Odds ratio (95% confidence interval) = 3.86 (1.63-9.30)

Ischemic heart disease: Odds ratio (95% confidence interval) = 5.12 (0.96-36.08)

Dyslipidemia: Odds ratio (95% confidence interval) = 4.35 (1.36-14.76)

In the present study the mean(±SD) total cholesterol was 208.56±42.16mg/dl,mean(±SD) low density lipoprotein was 132.78±42.59 mg/dl, mean(±SD) high density lipoprotein was 36.71±7.27 mg/dl, and the mean(±SD) triglyceride was 188.31±76.5 mg/dl among the cases (Table-III).

In sub-group analysis, significantly high levels were seen in both male cases compared to controls (16.23±7.58 μmol/L vs. 12.12±3.76 μmol/L, P<0.05) as well as female cases compared to controls (15.16±9.02 vs. 10.77±4.19 P<0.05). Significant (p<0.05) difference was found between cases and controls in unpaired t test regarding sex difference. (Table-IV)

Table III

Mean distribution of fasting lipid profile (mg/dl) of the study subjects (n=120).

Fasting lipid profile	Case (n=60)		Control (n=60)		P
(mg/dl)	Mean	±SD	value	±SD	value
Total cholesterol	208.56	±42.16	160.9	±21.5	0.001^{S}
Low density lipoprotien	132.78	±42.59	116.8	±8.5	0.005^{S}
High density lipoprotien	36.71	±7.27	39.7	±6.83	0.001^{S}
Triglyceride	188.31	±76.5	130.8	±11.7	0.001^{S}

S= significant

P value reached from unpaired 't' test

Table IV

Association of sex on serum homocysteine level among study subjects.

	Serum Homocysteine level (mg/dl+SD)		
Sex	Case (n=60)	Control (n=60)	P
	Mean±SD	Mean±SD	Value*
Male	16.23±6.26	12.12±3.76	0.021*
Female	15.16±9.02	10.77±4.19	0.005*

*=Significant.

P value reached from Chi square test.

Serum homocysteine level was high in both younger age group, (16.52±10.36 μmol /L vs. 11.66±4.22 μmol/L, P<0.05) and older age group of patients (15.02±4.79 μmol/L vs. 11.36±3.88 μmol/L, P<0.001) compared to the controls (Table-V).

In hypertensive subject the mean (±SD) serum homocysteine level was 16.62±6.6 μmol /L and 9.34±4.11 μmol/L in case and control groups respectively. In normotensive subjects the mean (±SD) serum homocysteine level was 14.6±8.5 μmol/L and 12.02±3.82 μmol/L in case and control groups respectively.

The mean (±SD) serum homocysteine level was 16.56±6.08 μmol/L and 7.60±2.0 μmol in cases and controls respectively among smokers. In nonsmokers the mean (±SD) serum homocystiene level was 15.11±8.36 μmol/L and 11.84±3.95 μmol/L in cases and controls respectively (p<0.05). (Table VI).

Table V

Association of age on serum homocysteine level among study subjects.

Age	Case (n=60) Mean±SD	Control (n=60) Mean±SD	P Value*
Younger (<45 years)	16.52±10.36	11.66±4.22	0.035*
Older (>45 years)	15.02±4.79	11.36±3.88	0.001*

*=Significant.
P value reached from Chi square test.

Table VI

Association of major risk factors with serum homocysteine level among study subjects

Risk factors	Case (n=60) Mean±SD	Control (n=60) Mean±SD	P Value*
Hypertensive	16.62±6.6	9.34±4.11	0.001*
Normotensive	14.6±8.5	12.02±3.82	0.002ns
Diabetic	16.34±8.31	10.04±2.97	0.001*
Non diabetic	15.49±7.49	11.56±4.04	0.001*
Smoker	16.56±6.08	7.60±2.0	0.004*
Non smoker	15.11±8.36	11.84±3.95	0.013*
Dyslipidemia	16.45±6.81	10.66±3.74	0.003*
Non dyslipidemia	15.32±7.71	11.56±4.04	0.086ns

*=Significant. ns= not significant.

Table VII

Risk factors analysis for ischemic stroke (multiple logistic regression models) (n=120).

	B	S.E	df	Sig.	Exp(B)	95% CI for Exp(B)	
						Lower	Upper
Serum homocystiene	1.819	0.532	1	0.001	6.17	2.17	17.51
HTN	1.410	0.479	1	0.003	4.10	1.60	10.48
Smoking	2.128	0.606	1	0.001	8.39	2.56	27.51
Dyslipidemia	1.423	0.629	1	0.024	4.15	1.21	14.24
Constant	-1.634	0.378	1	0.001	0.20		

B - Regression coefficient, SE - standard error, df - degree of freedom, Sig - significance, Exp. (B) - Odds Ratio

To assess the risk of ischemic stroke due to elevated serum homocysteine, multiple logistic regression analysis was performed where ischemic stroke was the dependent variable, serum homocysteine was the independent variable and hypertension, dyslipidemia and smoking were the covariates. Results showed that an abnormal serum homocysteine had 6.17 (95% CI 2.17% to 17.51%) times increase in odds of having stroke. (Table-VII).

Discussion:

The study was carried out in the department of neurology, BSMMU, Dhaka. A total 120 subjects were studied. Of them 60 were ischemic stroke patients and 60 were normal healthy Individuals. The aim of this study was to find out the association of hyperhomocysteinemia with ischemic stroke.

In this study the age range was15 to70 years with mean ±SD= 49.5±11.8 in case and mean ±SD =50.1±11.6 in control group. The majority of patients were in 51 to 70 years of age. This study also shows that the incidence of stroke rises with the increase of age. Similar observation were obtained by Arif SM[19] and Banford J[20].

In the present study male to female ratio was 1:0.8. Male involvement was 20% higher than that of female. Higher incidence of male subjects was observed by a number of investigators[21,22].The male excess in our country is due to the fact that allocation of beds in our hospitals are not homogeneous. Male beds are more than the females in our hospital. Another reason may be the religious and socio- cultural background. As because it was a hospital based study, this may not reflect the actual ratio of the community.

Most of the patients came from low socioeconomic class, which was 45.0% in this study. Similar observations were obtained in an other study [18]. But in one study done in USA, the author has shown an increased incidence of stroke in upper class group[23].

In this study, out of all patients abnormal serum homocysteine levels were found in 38.3% cases. The mean(±SD) serum homocysteine level found was 15.64±7.58 μmol/L in cases and 11.49±3.99 μmol/L in control group with unadjusted Odds ratio of = 3.52 (95% confidence interval 1.35-9.35, $p<0.05$). Significant difference was found between case and control in unpaired t test ($p<0.05$).

The other series showed that higher concentration of serum homocysteine level in ischemic stroke patients. The mean serum homocysteine level was 16.80±6.71 μmol/L in ischemic stroke patients while in controls it was 12.03±4.68 μmol/L. Another study determined the relationship between plasma homocysteine and ischemic stroke in the Nigerian population[24,25,26].

In sub-group analysis, significantly high levels of homocysteine were seen in both male and female patients compared to their controls (16.23±7.58 μmol/L vs. 12.12±3.76 μmol/L, P<0.05) and 15.16±9.02 vs. 10.77±4.19, P<0.05) respectively. This observation is supported by other studies [27,28] .

Serum homocysteine was high in both younger age group of patients (16.52±10.36 μmol /L vs. 11.66±4.22 μmol/L P<0.05) and older age group patients (15.02±4.79 μmol/ L vs. 11.36±3.88 μmol/L P<0.001). Modi et al [27]found significantly high homocystiene in both younger age group (10.85 ± 2.38 vs. 8.32 ± 2.89 μmol/L; d.f. 37; 95% CI 0.92-4.14; p = 0.003) and older age group of patients (9.42 ± 1.92 vs. 7.69 ± 2.65 μmol/ L; d.f. 46; 95% CI 0.35-3.11; P = 0.02).The cause of hyperhomocysteinemia may be due to genetic abnormalities caused by cystathionine synthase deficiency in younger age group of patients [29].In this study cause of hyperhomocysteinemia in younger group was not evaluated.

In hypertensive subjects the mean(±SD) serum homocysteine level was 16.62±6.6 μmol /L and 9.34±4.11 μmol/L in case and control group respectively. In normotensive subjects the mean(±SD) serum homocysteine level was 14.6±8.5 μmol/L and 12.02±3.82 μmol/L in case and control group respectively.

In dyslipidemic subjects the mean(±SD) serum homocysteine level was raised compared to the control group [16.45±6.81 μmol /L and 10.66±3.7 μmol/L (<0.001)] respectively.

A positive correlation of hyperhomocysteinemia was observed in this study. The mean(±SD) serum homocysteine level was 16.56±6.08 μmol/L and 7.60±2.0 μmol in case and control respectively among smokers. In non-smokers the mean(±SD) serum homocystiene levels were 15.11±8.36 μmol/L and 11.84±3.95 μmol/L in cases and controls respectively (p<0.05) .These observations were supported by Modi et al [27] and Alkali et al [5].

Out of all patients of present series 38.3% were smoker (both current and past). In a study done by Ullah et al. (2002) showed 59.84% smoker among their stroke patients[30]. In a previous study found 50% of cerebral thrombosis patients were smoker in their study of risk factors[31].

In the present study 20% had diabetes mellitus among the cases [unadjusted odd ratio 4.75 (95% confidence interval 1.15-22.64, p<0.05)]. Sixty per cent of patients were hypertensive with unadjusted odd ratio (95% confidence interval) = 3.86 (1.63-9.30).Similar observations were found in Jalaluddin and Bhuiyan et al series [32,33].In the present study ischemic heart disease was found in 15% of ischemic stroke patients.

To assess the risk of ischemic stroke due to elevated serum homocysteiene, multiple logistic regression analysis was performed where ischemic stroke was the dependent variable,The serum homocysteine was the independent variable and hypertension, dyslipidemia and smoking as the

covariates. Result showed that an abnormal serum homocysteine had 6.17 (95% CI 2.17% to 17.51%) times increase in odds of having stroke.

Conclusion

Hyperhomocysteinemia is an important and independent risk factor for development of Ischemic stroke. Hypertension and smoking per se are important contributory factors for elevated serum homocysteine.

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Chronic Helicobacter Pylori Infection as A Risk Factor for Acute Ischemic Cerebral Stroke

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Abstract

Background: *Helicobacter pylori infection can cause platelet aggregation and induces a procoagulant activity. Infection with the bacteria Helicobacter pylori is an independent risk factor for ischemic cerebrovascular disease independent of other conventional risk factors. We conducted a study to quantify the risk of acute ischemic stroke associated with chronic Helicobacter pylori infection.* ***Methods:*** *Anti-H.pylori antibody(IgG) were detected by rapid chromatographic immunoassay to establish the chronic H. pylori infection in all consecutive strokes and consecutive controls, all over the age of 40 years.* ***Result:*** *The seropositivity of H. pylori was 66.10% in cases compared to 50.85% in controls. The Odd's ratio is 1.87 (>1).* ***Conclusion:*** *This result indicates a strong, independent association between Chronic H. pylori infection and the risk of acute ischaemic stroke. So, Chronic Helicobacter pylori infection should be regarded as a risk factor for acute ischaemic stroke.*

Introduction

Stroke is responsible for 9.5% of all death in the world and in UK, stroke causes 12% of all deaths[1,2]. It is the third leading cause of mortality in the world[2]. Mortality is about 30-40% in haemorrhagic stroke and 10-20% in ischemic stroke[1,2,3]. Among the 15 million people worldwide who suffer a stroke each year, at least 5 million suffer long lasting disability, approximately 4.6 million deaths annually[4,5] .

Recently, 3 infectious agents like Chlamydia pneumoniae, Helicobacter pylori and Cytomegalo virus have been implicated in the atherosclerotic process[6]. Helicobacter pylori is a Gram negative infectious organism that causes chronic gastric inflammation that may be eradicated by antibiotic therapy[6,7]. A surprising number of extra – gastrointestinal disease have been reported to be associated with H. pylori infection, including coronary heart disease and ischemic stroke[8,9,10] H. pylori infection can cause platelet aggregation and induces aprocoagulant activity. The prevalence of H. pylori strongly varies between developing and developed countries, where prevalence among adult

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is typically around 80-90% and <40% respectively[11]. Infection with the bacteria H. pylori is an independent risk factor for ischemic cerebrovascular disease independent of other conventional risk factors[12].

The cytotoxin associated gene-A (Cag-A) makes strains of H. pylori virulent and especially damaging to arteries[13,14,15]. H. pylori is present in a substantial number of carotid atherosclerotic lesion and is associated with features of inflammatory cell response. Significant association between Cag-A positive H. pylori strains and the presence of carotid plaque instability support their possible involvement in pathophysiology of atherosclerotic stroke[15,16]. Cytotoxin causes lipid per-oxidation in endothelial cells and platelet aggregation, responsible for thrombosis, inflammation and swelling, further restricting blood flow and increasing the chance of stroke[17].

This study include the serologic test to detect chronic H. pylori infection.

In developing countries, the prevalence of H. pylori infection is about 80-90% If H. pylori infection is established as a risk factor for stroke, it will be a red alert for us. In that case early detection & appropriate treatment of H. pylori infection may reduce stroke incidence in our country.

Aim and objectives:

The study was performed among Bangladeshi patients with stroke to find out whether chronic Helicobacter pylori infection is a risk factor for acute ischaemic stroke among Bangladeshi population.

Materials and methods:

The study was carried out in the Department of Neurology, Chittagong Medical College Hospital, Chittagong, Bangladesh, from June 2006 –January 2007. This study included 59 acute ischaemic stroke patients diagnosed by history, clinical findings and confirmed by CT scan of head within 1 week of attack. This study included 59 age and sex matched nonstroke population who underwent blood sample examination for assessment of chronic Helicobacter pylori infection were included as control. The control subjects and the cases who had a history of H. pylori eradication therapy within 1 month were excluded from this study. The cases who had a history of cardiac disease(Atrial Fibrilation, Valvular Heart disease, Prosthetic Heart Valve), recurrent stroke, haemorrhagic stroke were excluded from this study. All the risk factors were noted: hypertension, hyper-cholesterolaemia, cigarette smoking, diabetes mellitus, a previous history of myocardial infarction, atrial fibrillation, history of stroke or TIA. The study population underwent a diagnostic workup that included blood glucose, serum fasting lipid profile, serum creatinine. X-ray chest P/A view, ECG, Echocardiogram, CT scan of head and Anti H- pylori antibody(IgG) were done in all cases. But only Serum lipid profile, blood sugar and anti-H. pylori anti-body(IgG) estimation were done in control subjects. With all aseptic precaution 3 ml of blood were collected by venipuncture in 5 ml silicon evacuated tubes containing EDTA and send for serological examination of anti-H. pylori antibody. Blood sample will be taken within 7 days of onset of stroke from

the cases and then centrifugation of collected samples were done to obtain serum. Serum anti- H. pylori antibody(IgG) estimation done in all subjects (both cases and controls), detected by rapid chromatographic immunoassay.

All relevant information from history, clinical examination and investigations were collected in a predesigned data collection sheet. Collected data were compiled and appropriate analyses were done by using computer based software, Statistical Package for Social Science(SPSS). P value < 0.05 was taken as minimum level of significance.

Observation and results:

A total number of 59 cases and 59 age and sex matched control subjects were examined. A total number of 80 patients were interviewed to obtain 59 cases. Among them, 21 patients were excluded from the study due to presence of haemorrhagic stroke (6), noncooperation (5), cardio-embolic condition (2), recurrent stroke (3), H. pylori eradication therapy (3) and death of patient (2) respectively.

Control subjects were taken preferably from the family members of the study subjects. Some control subjects were taken from volunteer of similar age and sex. A total of 70 subjects were interviewed to select 59 controls. Among them, 11 were excluded from the study due to noncooperation (9) and H. pylori eradication therapy (2) respectively.

Fig.-1 shows the age distribution of study subjects. Mean age of the control group was 60.78±10.87 years and in case group it was 61.57±1o.72 years. Mean difference was not statistically significant. Majority of the subjects presented at fifth to sixth decade of life.

Table-I shows that males and females were almost equally distributed between control and case groups. Among cases 66.10% were male and 33.90% were female. Among controls 66.10% were male and 33.90% were female.

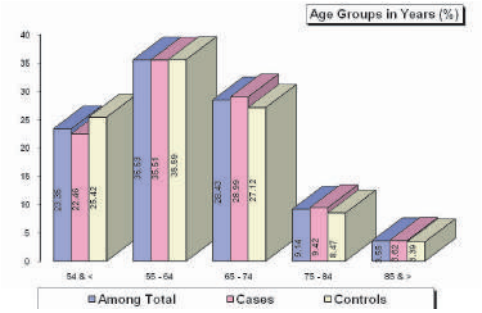


Fig.-1 : *Age distribution of study subjects*

Table-I

Statistics of categorical variables in relation to subjects with chi-square test results

		Subjects (N=197)				χ^2	df	*P*	Sig.
		Case (n=59)		Control (n=59)					
		No	%	No	%				
Sex	Male	39	66.10	39	66.10	0.006	1	0.532	NS
	Female	20	33.90	20	33.90				

N – Number of Subjects. χ^2 – Chi-Square value. df – Degree of Freedom.P – Probability value. Sig. – Significance. NS – Not Significant. S – Significant.

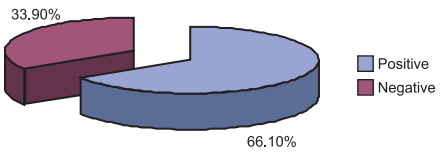
Table-II

Statistics of categorical variables in relation to subjects with chi-square test results

		Subjects (N=197)				χ^2	df	*P*	Sig.
		Case (n=59)		Control (n=59)					
		No	%	No	%				
Inhabitance	Urban	10	16.67	14	23.73	1.351	1	0.167	NS
	Rural	49	83.33	45	76.27				
Literacy Status	Literate	29	49.28	37	62.71	2.998	1	0.057	NS
	Illiterate	30	50.72	22	37.29				

N – Number of Subjects. $\times^2$ – Chi-Square value. df – Degree of Freedom.P – Probability value. Sig. – Significance. NS – Not Significant. S – Significant.

Anti-Helicobacter pylori antibody status among cases



Anti-Helicobacter pylori antibody status among cases

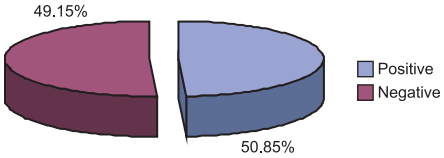


Fig-2: *Status of H. pylori seropositivity*

Table-II shows that among 59 cases 83.33% were living in rural areas and 16.67 % were in Urban areas. In controls 76.27% were living in rural areas and 23.73% in Urban areas. Among cases 68% were literate and among controls 62.71% were literate.

Fig.-2 shows that among 59 cases, 39 (66.10%) were H. pylori positive and 20(33.90%) were H. pylori negative, compared to 30 (50.85%) were positive and 29(49.15%) were negative out of 59 controls.

Table-III

Statistics of categorical variables (H. Pylori seropositivity) in relation to subjects with chi-square test results

H. Pylori status	Subjects (N=197)				χ^2	df	*P*	Sig.
	Case (n=59)		Control (n=59)					
	No	%	No	%				
Positive	39	66.10	30	50.85	3.974	1	0.034	*P*<0.05
Negative	20	33.90	29	49.15				

N – Number of subjects. χ^2 – Chi-Square value. df – Degree of freedom. P – Probability value. Sig. – Significance. NS – Not Significant. S – Significant. HS – Highly significant.

Table-III shows that among 59 cases, 39(66.10%) were H. pylori positive and 20(33.90%) were H. pylori negative, compared to 30 (50.85%) were positive and 29(49.15%) were negative out of 59 controls.

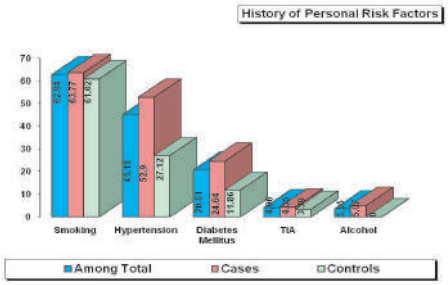


Fig.-3: *shows personal risk factors among cases and controls*

Fig.-3 shows among cases 52.90% were hypertensive, 62.77%, were smoker, 24.64% were diabetic 7% were alcoholic and 6% cases had history of TIA. But among controls 27.12% were hypertensive, 61.02% were smoker, 11.86% were diabetic, 2% cases had history of TIA. None of the control subjects were alcoholic.

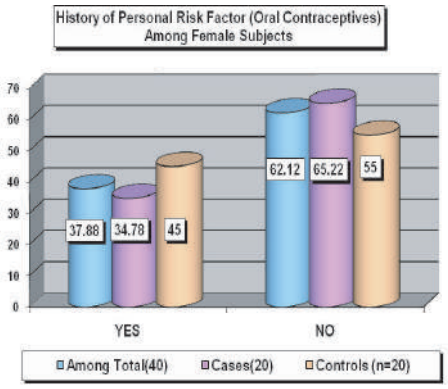


Fig.-4 shows history of personal risk factor Oral contraceptive pills among female subjects

Table-IV

Statistical analysis of categorical variables (Chi-Square Test)

History of Personal Risk Factors	N=118	Anti H. Pylori Antibody Status				χ^2	df	*P*	Sig.
		Positive		Negative					
		No	%	No	%				
Smoking	Yes	41	59.42	33	67.35	1.591	1	0.133	NS
	No	28	40.58	16	32.65				
Hypertension	Yes	31	44.93	22	44.90	0.010	1	0.520	NS
	No	38	55.07	27	55.10				
Diabetes Mellitus	Yes	12	17.39	13	26.53	2.274	1	0.093	NS
	No	57	82.61	36	73.47				
TIA	Yes	2	2.89	3	6.12	2.014	1	0.148	NS
	No	67	97.11	46	93.88				
Alcohol	Yes	3	4.35	1	2.04	0.307	1	0.449	NS
	No	66	95.65	48	97.96				

N – Number of subjects. χ^2 – Chi-Square value. df – Degree of freedom. P – Probability value. Sig. – Significance. NS – Not significant.

Table-V

Statistical analysis of continuous variables in relation to subjects with independent samples T – test results

		N	Mean	± SD	Range	t	df	*P*	Sig.
Age in Years	Total	118	61.34	10.75	40~90	0.47	195	0.636	NS
	Case	59	61.57	10.72					
	Control	59	60.78	10.87					
Systolic BP	Total	118	149.27	27.53	100~220	6.16	138	0.000	VHS
in mmHg	Case	59	155.95	27.20					*P*<0.001
	Control	59	133.64	21.41					
Diastolic BP	Total	118	88.19	12.34	65~20	6.00	195	0.000	VHS
in mmHg	Case	59	91.37	11.33					*P*<0.001
	Control	59	80.76	11.44					
Blood Sugar Level	Total	118	143.31	77.43	67~450	1.20	144	0.234	NS
in mg/dl	Case	59	145.27	79.43					
	Control	9	113.44	18.36					
Serum Creatinine	Total	68	1.09	0.34	0.5~2.6	5.58	18	0.000	VHS
in mg/dl	Case	49	1.11	0.35					*P*<0.001
	Control	7	0.81	0.11					
Serum Cholesterol	Total	56	205.23	45.96	116~371	- 0.10	95	0.923	NS
in mg/dl	Case	51	205.11	46.59					
	Control	6	207.00	38.39					
Serum LDL	Total	57	130.80	35.37	51~291	0.40	95	0.689	NS
in mg/dl	Case	51	131.18	36.30					
	Control	6	125.17	16.36					
Serum HDL	Total	57	42.37	8.56	27~75	0.21	95	0.836	NS
in mg/dl	Case	51	42.42	8.53					
	Control	6	41.67	9.73					
Serum TG	Total	57	156.43	73.19	40~390	- 0.89	95	0.377	NS
in mg/dl	Case	51	154.74	71.03					
	Control	6	182.17	105.72					

N–No. of subjects. SD–Standard deviation. t–Student's t value. df–Degree of freedom.P–Probability value. Sig.–Significance. NS–Not significant.VHS–Very highly significant

Discussion

This was a hospital based study and was carried out to see the association of chronic H. pylori infection as a risk for ischaemic stroke. The study subjects were taken from the department of neurology, Chittagong Medical College Hospital, Chittagong. During the study period (from June 2006 to January 2007) 59 patients, diagnosed as ischaemic stroke clinically and confirmed by CT scan of head, were evaluated. Age, sex and socioeconomic status matched 59 respondents were also taken as control.

In the study, majority (35.53%) of the subjects were in between 55-64 years of age. Different previous study showed majority of the patients were aged between 50-59 years (35%)[18,19]. In this study, mean (±SD) age was 61.57±10.72 years. Similar past studies had comparable age (58±12years) of the patients[20].

In this study 66.10% were male and 33.90% were female. The male to female ratio was 2:1. Males involvement was higher than females. This difference may be due to the socio-cultural stigma prevailed in our country for which females are not generally brought to hospital for treatment.

Majority of study subjects were rural (81.2%) inhabitance. This may be due to the fact that majority of the urban patients were treated in Private Clinic and Doctor's chamber. This study showed majority of study subjects were retired persons (19.8%), businessmen (19.8%) and housewifes (19.8%).

In the present study, 63.77% stroke patients were smoker among them 50% were male and 13.77% were female. In two previous studies 66.67%[21] and 68.30%[22] stroke patients were smoker. This may indicate changeable pattern of smoking habit among our population.

Diabetes Mellitus were present in 24.64% of stroke patients which had similarity with two previous studies, where 25%[19] and 30%[23] patients were diabetes respectively.

Hypertension was present in 52.90% of stroke patients in this study. This is close to many other studies[19,22], done previously.

In this study 12.32% stroke patients had family history of stroke. It is slightly lower than one previous study (18.50%)[18]. This may be due to increase awareness of the population about prevention of stroke and increase awareness of diabetes mellitus and hypertension.

History of TIA was found in 4.35% of stroke patients. Alcohol intake (3.6%) is another risk factor, which is not common in our society. Only seven male patients were alcoholic in this study.

Oral contraceptive pill (OCP) is a common risk factor for young females. In this study, history of taking OCP present in 11.59 % of cases and 15.25 % of control subjects. It is higher then a previous study where it was 5.71%[21]. This difference may be due to good impact of family planning program in our society.

In this study, Table-III shows that seropositivity of H. pylori is 66.10% in cases compared to 50.85% in controls. Different studies showed that H. pylori seropositivity in stroke patients were about 72.5% (in cases) and 56.4% (in controls)[17], and 69% (in cases) and 58.5% (in control)[24], 66.7% (in cases) and 40% (in control)[23] . In this

study the Odd's ratio is 1.87 (> 1). This value proved that chronic H. pylori infection is a risk factor for acute ischaemic stroke.

According to executive summary of the report of the National Cholesterol Education Program (NCEP), desirable serum total cholesterol is <200mg/dl and LDL-cholesterol level is <100mg/dl. In this study, mean (±SD) serum LDL-cholesterol was 131.18±36.29mg/dl in case group compared to 125±16.36mg/dl in control group. In H. pylori positive subjects, both serum cholesterol and LDL-cholesterol were higher in both in cases and controls, 205.36±53.66 and 132.45±37.87mg/dl respectively.

Cardioembolic ischaemic strokes were excluded from the study by clinical examination and as well as by echocardiographic examination. Some mechanism may link chronic H. pylori infection with atherogenesis, immune-mediated mechanism and free radical formation. Chronic H. pylori infection result in a low grade chronic inflammatory process in vascular endothelium[25]. This chronic inflammatory process causes injury of the endothelial cells and infiltration of Inflammatory cells in subendothelial tissue and enhance the deposition of lipid-containing macrophages in tunica media.

All these processes promote atherosclerosis and also causes instability of preformed atherosclerotic plaques. This process involves internal carotid arteries as well as other intracranial large and small vessels. When an atherosclerotic plaque becomes instable, then it may cause atheroembolic ischaemic stroke.

Helicobacter pylori infection causes hyperhomocysteinaemia and enhance atherogenesis. Chronic H. pylori infection modify total serum cholesterol and LDL-cholesterol concentrations in a way that increases the risk of atherosclerosis and these changes occur specially with more virulent CagA positive strain infection[15].

Chronic H. pylori infection increases the plasma fibrinogen concentration significantly and causes a procoagulant state. Plasma fibrinogen was significantly higher in H. pylori positive stroke patients than in H. pylori negative controls[26].

Infection-related chronic inflammation from H. pylori infection may increase CHD risk, because the CHD risk factors, plasma fibrinogen, C-reactive protein, and blood leukocyte count have been elevated in seropositive subjects[27].

There are evidence of molecular mimicry between the CagA antigen and vascular wall peptides. This finding yields biological plausibility to the theory that H pylori infection may play a role in the pathogenesis of atherosclerosis[28].

LDL inhibit lipid peroxidation and oxidative modification of LDL. Modified LDLs are atherogenic[29]. Reactive oxygen species and that oxidative stress might be implicated in promoting a low-grade systemic inflammation[30].

Considering all the above observations, it is established that this study showed a close relationship between the seropositivity of Helicobacter pylori infection and ischaemic cerebral stroke.

Conclusion:

Infection is the newly identified risk factor for ischaemic stroke. H. pylori infection

can cause platelet aggregation and induces a procoagulant activity. There are association between chronic H. pylori infection and ischaemic stroke. It may be concluded that chronic Helicobacter Pylori infection is a risk factor for ischaemic stroke among Bangladeshi population. Further, long-term study with large sample size may help to determine the role of Helicobacter Pylori infection in ischaemic stroke

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Serum Uric Acid Level Among Male and Female Patients with Ischemic Stroke Admitted in a Tertiary Level Hospital of Bangladesh

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Abstract

Background: *The role of serum uric acid (SUA) in ischemic stroke and cardiovascular disease is still not clear. The present study was conducted to find out the level of serum uric acid among the patients with ischemic stroke admitted in Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital, Dhaka, Bangladesh.* ***Methodology****: This cross sectional study was carried out in the Department of Neurology, BSMMU during the period of January 2007 to December 2008. A total of 60 subjects with ischaemic stroke were included in this study. Data were collected purposively. Statistical analyses Univariate and bivarite analysis was performed. Chi square test was done. Probability value <0.05 was considered as level of significance and 95% confidence limits were taken. Hyperuricemia or abnormal SUA is most commonly defined by plasma uric acid concentrations greater than 7.0 mg/dl (0.42mmol/L) in men or greater than 6.0 mg/dl (0.36mmol/L) in women.*

Result: *The mean ±SD age of the patients was 62.05 ± 9.86 years. Most of the patients were in 5th (33.3%) and 6th (36.7%) decade. Out of 60 patients 68.3% were male and 31.7% were female. Male and female ratio was 2.16:1. Mean (±SD) SUA level was 4.94 (±1.76). Out of 60 patients with ischaemic stroke, 46 patients (76.7%) had normal level of SUA and 14 patients (23.3%) had abnormal SUA. Among the patients with abnormal SUA 9 were male and 5 were female. There was no statistically significant difference in abnormal SUA among the male and female stroke patients were found (>0.05).* ***Conclusion:*** *Elevated SUA is not uncommon in patients with ischemic stroke. But there was no significant difference of SUA among male and female patients. Further large scale studies are needed to examine the present observation.*

Key word: Stroke, Cross sectional study, Serum Uric Acid, Bangladesh.

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Introduction:

Stroke is the most common cause of disability and a leading cause of mortality worldwide. Though the incidence is falling in the West but probably it is rising in Asia[1]. About one-fifth of patients with stroke dies within a month of the event and half of those who survive face physical disability[2]. Its consequences are myriad ranging from physical disability to death, to psychological, social and economic consequences. These consequences do not only affect the individual or his/her family but also society as a whole[1]. According to the World Health Organization 5.5 million people died of stroke in 2002, and roughly 20% of these deaths occurred in South Asia[3]. Contrary to decline in the incidence of the disease in the western population, the burden of the disease in South Asian countries (India, Pakistan, Bangladesh, and Sri Lanka) have inclined and is expected to rise[4].

The treatment of stroke is still quite unsatisfactory, and new ways to improve the recovery and prognosis are needed[5]. For many years, serum uric acid (SUA) has been used in clinical practice as a marker of several metabolic disturbances[6]. But the role of SUA in ischemic stroke and cardiovascular disease is still not completely understood[7]. It is a major product of the catabolism of purine nucleotides that are the principal constituents of cellular energy stores, such as ATP and components of DNA and RNA. SUA level varies significantly due to increase generation, such as high purine or protein diets; alcohol consumption, conditions with high cell turnover, or enzymatic defects in purine metabolism and due to decrease excretion such as reduction in glomerular filtration rate (GFR)[8,9].

High serum uric acid or hyperuricemia has been suggested as a possible risk factor for hypertension, metabolic syndrome, and cardiovascular disease, independent of the traditional risk factors. Hyperuricemia or abnormal SUA is most commonly defined by plasma uric acid concentrations greater than 7.0 mg/dl (0.42mmol/L) in men or greater than 6.0 mg/dl (0.36mmol/L) in women[10]. There is a potential pathogenetic mechanism to explain why an elevated SUA at the time of stroke may be injurious[11]. Several major epidemiological studies have shown that high SUA concentrations are an important predictor of cardiovascular disease or events such as hypertension, myocardial infarction and stroke[6].

A large number of studies have been performed to identify the relationship between serum uric acid and stroke but the issue remains unresolved and it is not clear whether the correlation between uric acid and stroke is circumstantial or causal[12]. Some studies have found serum uric acid is a predictive for the development of cardiovascular disease whereas others have failed to identify serum uric acid as a significant and independent risk factor after controlling for other atherosclerotic risk factors. It still remains controversial whether elevated serum uric acid is neuroprotective or injurious at the onset of stroke[13].

There was no community based epidemiologic study on stroke in Bangladesh. In Pakistan estimated annual incidence is 250 per 100,000, translating to 350,000 new cases every year[14]. A recent community survey in Kolkata, India carried out by the Indian Council of Medical Research, showed the average annual incidence of stroke as 145 per 100,000

persons per year[15]. This rate is much higher than those reported previously from other parts of India. In China, the total average age-adjusted incidence of first-ever stroke ranged from 116 to 219 per 100,000 per year[16]. Though the exact statistics of incidence and prevalence of stroke in Bangladesh is not available but the number of such kind of problem is increasing day by day[17]. The present study was conducted to find out the SUA level in the patients with ischemic stroke who were admitted in a tertiary level hospital of the capital city of Bangladesh.

Materials and methods:

The present cross sectional study was conducted to explore whether there is any association between SUA and the ischemic stroke among the patients admitted in the Department of Neurology, BSMMU, Dhaka during the period of January 2007 to December 2008. A total of 60 patients with ischaemic stroke were included in this study. In this study hyperuricemia or abnormal SUA was defined by plasma uric acid concentrations greater than 7.0 mg/dl (0.42 mmol/L) in men or greater than 6.0 mg/dl (0.36 mmol/L) in women.

Patients with (WHO defined) stroke, ischemic in type, confirmed by CT scan of head and/or MRI of brain and within 4 weeks of attack, aged over 40 years and gave consent and was willing to comply with the study procedure were included as participant in the present study. Patients were excluded from the study who refused to participate, seriously ill, having abnormal cardiac condition giving rise to stroke like valvular heart disease and atrial fibrillation and with history of joint pain or vascuitis. Socio-demographic data (age, sex, smoking habit, was collected by semi-structured questionnaire in face to face interview. Information was collected by taking medical history and clinical examination and subsequent laboratory investigations. Informed written consent was taken before collecting data. For all study subjects 5 ml fasting (10-12 hours) venous blood sample was collected from the median cubital vein by disposable plastic syringe with all aseptic precaution. Then blood was immediately transferred to a dry clean glass test tube and allowed to clot. Serum was separated after adequate centrifugation. Separated serum was collected into plastic micro centrifuged tubes and appropriately labeled and stored in ultra freezer until analytical measurement of serum. Then serum uric acid was measured in Biochemistry Department, BSMMU by autoanalyser Backman Coulter, Synchron CX9, and Clinical System ALX.

Descriptive and bivariate statistics were performed. Frequency, percentage, mean and standard deviation (SD), cross tabulation and Chi square test was performed. 95% confidence limits were taken. Probability value <0.05 were considered as level of significance. Windows based computer software devised with Statistical Packages for Social Sciences (SPSS-15) (SPSS Inc, Chicago, IL, USA) was used. Ethical approval was taken from the Institutional Ethical Review Committee of BSMMU.

Results:

The mean ±SD age of the patients was 62.05 ± 9.86 years. Most of the patients were belong to 5th (33.3%) and 6th (36.7%) decade . Out of 60 patients 68.3% (41) were male and 31.7% (19) were female.

Table-I

Distribution of the respondents by different characteristics

Age	Frequency	Percent
41-50	06	10.0
51-60	20	33.3
61-70	22	36.7
>70	12	20.0
Mean ± SD (range)	62.05 ± 9.86 (42-85)	
Sex		
Male	41	68.3
Female	19	31.7
Status of smoking		
Present	42	70.0
Absent	18	30.0
Type of smoker		
Current	37	88.1
Past	05	11.9
History of betel nut and/tobacco chewing		
Present	38	63.3
Absent	22	36.7
Diabetes mellitus		
Present	20	33.3
Absent	40	66.7
Hypertension		
Present	34	56.7
Absent	26	43.3

Male and female ratio was 2.16:1. Among the respondents 70.0% were smoker (both current and past) and 30.0% were non-smoker. Among the smokers current and past smokers were 88.1% and 11.9% respectively. Nearly two-third (63.3%) respondents had history of betelnut and tobacco chewing and one-third participants were diabetic and 56.7% were hypertensive (Table-I). Among the 60 cases 46 (76.7%) patients had normal level of SUA and 14 cases (23.3%) had abnormal SUA (Fig.-1). Out of 41 male with ischaemic stroke 9(19.9%) had abnormal SUA and out of 19 female with ischaemic stroke 5(26.3%) had abnormal SUA. Mean (±SD) SUA level was 4.94 (±1.76) (Table-II). There was no statistically significant difference in SUA among the male and female patients (>0.05) (Table-III).

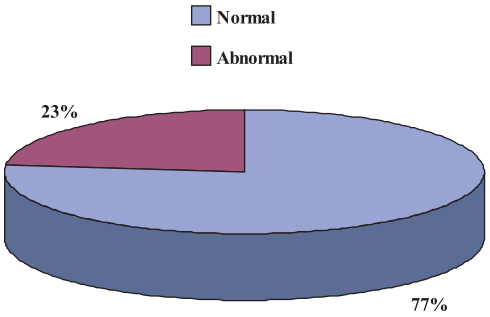

Fig.-1: *Distribution of the respondents by serum uric acid*

Table-II

Distribution of the respondents by level of serum uric acid and sex (n-60)

Serum uric acid	Male Frequency (%)	Female Frequency (%)	Total Frequency (%)
<6.0 mg/dl	22(53.7)	14(73.7)	36(60.0)
6.0-7.0 mg/dl	10(24.4)	02(10.5)	12(20.0)
7.0-8.0 mg/dl	05(12.2)	02(10.5)	07(11.7)
> 8.0 mg/dl	04(09.7)	01(05.3)	05(08.3)
Total	41(100.0)	19(100.0)	60 (100.0)
Mean ± SD	4.66±1.62 mg/dl		

Table-IV

Distribution of the serum uric acid by sex

Serum uric acid	Sex		P value*
	Male	Female	
Normal	32(78.0)	14(73.7)	0.712
Abnormal	09(22.0)	05(26.3)	
Total	41(100.0)	19(100.0)	

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

Discussion:

Several major epidemiological studies have shown that high SUA concentrations are an important predictor of cardiovascular disease or events such as hypertension, myocardial infarction and stroke[6]. The mean ±SD age of the ischemic stroke patients in this study was 62.05 ± 9.86 years. Most of the cases belonged to 5th (33.3%) and 6th (36.7%) decade. The mean age of patients with stroke varies from 52-66 years in various studies and the male to female ratio was about 2.16:1. Elderly people are the most vulnerable group for developing stroke. In a study conducted in Bangladesh it was seen that in both hemorrhagic and ischemic stroke most of the sufferers were in the 51-60 years age group[17].

Male and female ratio of stroke patients was 2.16:1, indicating that stroke is a male predominant disease. In a similar study conducted by Khan[18] the ratio of male and female was found 2.75:1. Another study by Hannan[19] found male and female ratio was 2.53:1 in stroke patients irrespective of types.

In this study, 70.0% were smoker (both current and past) and 30.0% were non-smoker. Among the smokers 88.1% and 11.9% were current and past smoker respectively. In one study by Jalaluddin[19] found 54.0% of stroke patients were smokers. Similar result was found by another study by Somay et al[20]. Khan[12] found that 55% of ischemic stroke patients were smoker. Significant association between ischemic stroke and smoking habit was observed in that study which differs from the present study. In this study 63.3% had history of taking of betelnut and tobacco chewing.

Around one-third patients had diabetes mellitus. Patients with non–insulin-dependent diabetes mellitus (NIDDM) are at increased risk for stroke. Hyperuricemia is a common finding in NIDDM, but its significance as an independent risk factor for cardiovascular disease has remained uncertain[21]. In a population-based study Lehto et al.[22] found that serum urate as a predictor of stroke in NIDDM patients free of clinical nephropathy; and hyperuricemia was a strong predictor of stroke in middle-aged patients with NIDDM independently of other cardiovascular risk factors. In Jalaluddin[19] series, 20% of ischaemic patients were diabetic.

In the present study out of 60 patients 56.7% had hypertension. Wang et al.[23] examined the relation of serum creatinine and uric acid to mortality and cardiovascular disease in older (aged 60 years) Chinese patients with isolated systolic hypertension (systolic/diastolic

blood pressure 160/<95 mm Hg). In their study they found that older Chinese patients with isolated systolic hypertension, serum creatinine and serum uric acid were predictors of mortality. About 60% of patients with ischemic stroke were hypertensive in Jalaluddin series[19]. Similar results were obtained in other studies[24-26].

Although high SUA concentrations have been identified as an important risk marker for stroke in unselected populations in a number of epidemiological studies, it is unclear whether high SUA levels promote or protect against the development of stroke, or simply act as a passive/ circumstantial marker of increased risk[27-29]. Independently of other prognostic factors, higher serum urate levels predicted poor outcome (dead or in care) and higher vascular event rates and the role of urate in stroke pathophysiology remains uncertain, but intervention to lower urate may be worth considering[28]. In the present study out of all patients 46(46.7%) had normal level of SUA and 23.3% had abnormal SUA. Mean (±SD) SUA (mg/dl) level was 4.94 (±1.76). Out of 41 males with ischaemic stroke 9 had abnormal SUA and out of 19 females with ischaemic stroke 5 had abnormal SUA. In the present study there was no statistically significant difference in serum uric acid level among male and female patients (>0.05). In Milionis et al.[29] series stroke patients showed higher concentrations of SUA (5.6 ± 1.7 mg/dl). Serum urate concentration is associated with cardiovascular disease, and hyperuricemia predicts first-ever stroke. Weir et al.[27] found that elevated urate level predicted a lower chance of good 90-day outcome (odds ratio, 0.78 per additional 0.1 mmol/L; 95% confidence interval [CI], 0.67 to 0.91) independently of stroke severity and other prognostic factors. Vascular event risk increased with urate level (relative hazard, 1.27 per additional 0.1 mmol/L; 95% CI, 1.18 to 1.36). Higher urate levels have a greater effect on vascular event rates in the presence of diabetes (additional relative hazard, 1.22 per additional 0.1 mmol/L; 95% CI, 1.06 to 1.41). The results of this study suggest that abnormal SUA is not uncommon findings among the patients with ishchemic stroke in the tertiary level hospital of Bangladesh.

Conclusion:

Elevated serum uric acid concentration is not an uncommon finding in patients with ischaemic stroke. Further large scale studies are required to examine the pattern of SUA among the patients of stroke.

Limitations of the study:

In the present study conducted with a small sample size and data were collected from one neurology centre in Dhaka city. Therefore the sample may not be representative for the whole population.

Recommendation:

Traditional risk factors such as hypertension, diabetes and dislipidaemia are now being treated more aggressively after ischemic stroke following the results of the Perindopril Protection Against

Recurrent Stroke Study and Heart Protection Study. However, there is a pressing need to identify additional treatable factors that are associated with ischaemic stroke and easily measurable and highly prevalent in the general population. More research is needed to examine whether hyperuricemia is a risk for ischemic stroke in Bangladeshi people.

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Interictal Electroencephalography in Epilepsy: A Tertiary Centre Experience

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Abstract

This study was done to compare the clinical diagnosis of epilepsy with the efficiency of interictal electroencephalography (EEG). It was quasi-experimental and comprised of 100 patients of epilepsy and 50 healthy adults as control. The mean (±SD) age of epilepsy patients were 19.98±10.07 years. Male patients were 67%. Only 3% of epileptic patients had the positive family history of epilepsy. Generalized tonic clonic seizure was the major (79%) form of clinical presentation. The second common diagnosis was focal epilepsy with secondary generalization (33%). Finally the diagnostic efficacy of electroencephalography as conventional tool was compared with clinical observations. The study found that sensitivity of EEG was 74%, specificity was 94%, positive predictive value was 96%, negative predictive value was 62.7% and its accuracy was 80.6%. The differentiation was statistically significant between EEG findings and clinical diagnosis.

Introduction

Seizures result from paroxysmal and abnormal excessive electrical neuronal discharges in the brain that cause a variety of clinical manifestations. The term "epilepsy" is usually restricted to those cases with a tendency for recurrent seizures[1].

Epilepsy may be defined as a sudden recurrent transient paroxysmal excessive abnormal discharge of a group of cerebral neurons giving rise to either motor and/or sensory and/or autonomic and/or psychic symptoms with or without loss of consciousness.

Epilepsy is a relatively common neurological disorder. From many studies around the world it has been estimated that the mean prevalence of active epilepsy (i.e. continuing seizures or the need for treatment) is approximately 8.2/1000 of the general population[1].

In Bangladesh exact prevalence of epilepsy is not known, because no such demographic survey has been carried out so far. According to WHO study group report, the prevalence in Bangladesh is also high (WHO, 1978), which was corroborated 6.7/1000 population. No current data regarding incidence of epilepsy in Bangladesh is available. It is assumed that the current incidence in Bangladesh is 120-140/100000 population[2].

Worldwide there are 3.5 million new cases of epilepsy per year, of them 40% occurs in children, 40% in adults and 20% in elderly. In developed countries the most common cause of non-idiopathic seizure is stroke accounting for around 14% of cases. Idiopathic causes are responsible

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for at least 50% of cases worldwide[3,4]. One of the main reasons for the higher incidence and prevalence of epilepsy in developing countries is the higher risk of experiencing a condition which can lead to permanent brain damage. These conditions include meningitis, malaria, pre and perinatal complications, malnutrition, infections including multiple parasitisms[1].

The diversity of symptoms that can result from an epileptic seizure arises from different brain regions and they give rise to the particular features of an individual seizure. In spite of the technologic advances that have contributed to the understanding and treatment of epilepsy, still now types of epilepsy and selection of treatment relies on the observed details of the seizure phenomenology. In this regard, obtaining an accurate seizure history from the patient is essential. The initial evaluation in patients who present with seizures is to determine whether these episodes are epileptic in nature or not. A false diagnosis can have severe repercussions for the patient, including the expenses of medications as well as their potential adverse effects. Other hazards include the loss of driving privileges, loss of income, and the expenses[5]. Also abnormal interpretation of epileptiform discharge or normal EEG provide extra burden to the patient.

The diagnosis of epilepsy and it's types are based mainly on the history, EEG acts as a supportive tool. EEG records cerebral activity only during the time of recording and so its information is thus only a snapshot in time. It therefore cannot confirm the diagnosis of epilepsy in all patients with epilepsy. However with all these procedures EEG fails to detect epileptiform discharges in 20-30% of epileptic patients. Abnormal EEG patterns may occur with a number of different conditions, not just epilepsy e. g. head trauma, stroke, brain tumour, or seizures. A common example of this type is called "slowing" of waves [6]. So, EEG acts as a supportive diagnostic tool and sometimes confused the diagnosis of epilepsy if proper clinical history is not determined. To maximize the value of the EEG it is important to obtain a baseline recording early in the course of this disorder and before the beginning of any treatment.

The present study evaluates the accuracy of EEG as a diagnostic tool for epilepsy in Bangladeshi patients. In this study patients are broadly diagnosed as primary generalized epilepsy and localization related epilepsy on the basis of definite clinical parameter. They are further EEG classified as having generalized epileptiform discharge, focal epileptiform discharge and normal background.

The comparison of clinical diagnosis of epilepsy with that of EEG is done in terms of sensitivity, specificity and accuracy. Because each abnormal EEG pattern can be caused by more than one disease and some diseases cause more than one abnormal EEG pattern, the EEG alone can not be used to make a specific clinical diagnosis[6]. Even so, the EEG becomes a powerful diagnostic tool when it is used in combination with the clinical history, physical examination and other laboratory information.

In developing country like Bangladesh EEG is a costly investigation and has limited access. But in developed country most

medium sized hospital has its unrestricted access. In UK, a study showed that 50 to 60% of referring doctors thought that the procedure could diagnose or exclude epilepsy [7]. In another study they found that results of EEG influence management in only 3% cases. They revealed reasons for requesting EEG varied between clinicians, while neurologist concentrated on patients with epilepsy and seizures (62%), other doctors used the procedure as diagnostic tool [8].

There was no such study regarding sensitivity, specificity and importance of EEG and its accuracy in determining its role in Bangladeshi patients. This study was carried out to evaluate the efficacy and feasibility of EEG for the diagnosis of epilepsy in Bangladeshi epileptic patients.

Methodology

Study design:

This was a quasi-experimental study.

Duration of study:

Data were collected from July 2006 to June 2007.

Study place:

This study was done in epilepsy clinic of Dhaka Medical College Hospital. Patients who attended the epilepsy clinic of Dhaka Medical College were selected. Subjects were drawn purposively from study population according to the compliance of exclusion and inclusion criteria. Healthy age and sex matched 50 people were also selected to validate the study.

Clinical diagnosis was made by two consultant neurologists not below the rank of assistant professor in blinded fashion. The patients who had clinical diagnosis of epilepsy, agreed by both the neurologists, were included in the study. The EEG recording was interpreted also by two expert efficient EEG interpreters who were blinded about the study. The EEG report having the common agreement by two experts was taken as valid report.

Well furnished and equipped epilepsy clinic is capable of providing all the necessary logistic support. Nihon kohder electroencephalograph (EEG-9200J/K) shielded electrodes were used, there was also accurate event time input, automatic photic stimulation and 64 traces can be displayed if needed. Calm and quiet place for EEG recording was maintained. Both aware and stage I sleep EEG were done.

The categorical variable was expressed in terms of percentage or proportion. The difference in the percentage or proportion was tested for significance by non-parametric test, such as chi-squared test. The statistical analysis was done by SPSS version 11.5. The p value < 0.05 was considered as significant.

Ethical issues

Patients who were selected were informed about the nature of the study. The patients were assured about confidentiality and anonymity. They were informed about the diagnostic test- EEG. Written consent was taken from patients or their legal guardian.

Results

This study was carried out to evaluate the efficacy and feasibility of EEG for the diagnosis of epilepsy. One hundred patients of epilepsy were recruited in the study. Two consultant neurologists diagnosed the patients clinically before inclusion. Fifty healthy age and sex matched subjects were also chosen for the study.

In the study subjects with the diagnosis of epilepsy they were between the ages 20-43 years. Male were about twice than that of female. The difference in percentage of sex and age between the groups were not statistically significant ($p>0.05$). Regarding the socioeconomic status, most of the epileptic patients came from lower income group (income <50,000/yr). None of the control group had positive family history of such disease.

Generalized/ tonic-clonic contraction was major (79%) form of presentation. Myoclonic jerk (2%) was rare form in the study subjects. A little over one-third patients (35%) presented clinically with froothy sputum.

Table-I

Demographic characteristics of study subjects

Demographic characteristics	Study group	
	Epilepsy (n=100)	Control (n= 50)
Sex		
Male	67	32
Female	33	18
Age in years		
Mean ±SD	19.00+9.2	19.98+10
< 20 years	66	33
20-35 year	28	12
>35 year	6	5
Family income per year in Tk.		
<50,000	77	25
50,000 -100,000	21	23
>100,000	2	2
Family history of epilepsy		
Present	3	0
Absent	97	50

Table-II

Clinical features

Parameters	Outcome	Percentage	χ^2 value	p value
Generalized tonic-	Absent	21	33.64	<0.001
clonic contraction	Present	79		
Myoclonic jerks	Absent	98	92.16	<0.001
	Present	2		
Tongue biting	Absent	65	9.04	0.003
	Present	35		
Froothy sputum	Absent	61	4.84	0.28
	Present	39		
Screaming	Absent	83	43.56	<0.001
	Present	17		
Urinary incontinence	Absent	67	11.56	<0.001
	Present	33		
Sudden fall	Absent	86	51.84	<0.001
	Present	14		
Sudden anxious and	Absent	91	76.24	<0.001
frightened	Present	9		
Movement of limb	Absent	74	23.04	<0.001
	Present	26		
Spontaneous activity	Absent	94	77.44	<0.001
	Present	6		

Primary generalized epilepsy was the major (45%) clinically diagnosed epileptic disorder. The difference of percentage of different type of clinical diagnosis was statistically highly significant ($p<0.001$).

Table-III

Clinical diagnosis

Clinical diagnosis	Percentage	χ^2 value	p value
Primary generalized tonic-clonic epilepsy	45		
Focal epilepsy with secondary generalization	33		
Simple partial seizure	11		
Complex partial seizure	5	97.28	
Absence epilepsy	4		
Myoclonic epilepsy	2		

The EEG diagnosis was further categorized into normal, generalized epileptiform discharge and focal epileptiform discharge and clinical diagnosis was categorized in primary generalized epilepsy and focal epilepsy. Of the 26% false negative diagnosed cases, 8% was of primary clonic-tonic epilepsy and 18% was of focal epilepsy.

The validity of a test is the function of the sensitivity, specificity and the accuracy of the measuring tool. The sensitivity is the percentage of positive case diagnosed by the EEG from the disease group assessed by clinical examination. Positive predictive value (PPV) of the test is the percentage of positive test that have the disease and the negative predictive value (NPV) is the percentage of negative test that have no disease.

Table-IV

Comparison of the interictal EEG diagnosis with clinical diagnosis

Category of EEG diagnosis	Category of clinical diagnosis			χ^2 value	p value
	Primary tonic clonic	Focal	Total		
Normal	8	18	26	24.04	<0.001
Generalized epileptiform discharge	20	2	22		
Focal epileptiform discharge	17	35	52		
Total	45	55	100		

Table-V

The validity of EEG in comparison of clinical diagnosis

Diagnosis by EEG	Clinical Epileptic	diagnosis Healthy	Total (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
Positive	74	3	77	74	94	96	62.7	80.6
Negative	26	47	73					
Total	100	50	150					

Table-VI

Comparison of clinical diagnosis and EEG findings between two groups

EEG findings	Clinical diagnosis		P value
	Case (n=100)	Control (n=50)	
Positive	74	3	0.001
Negative	26	47	
Total	100	50	

In EEG findings the differentiation was statistically significant (P<0.05) between two groups

Discussion

This study was conducted to evaluate the efficacy and feasibility of EEG for the diagnosis of epilepsy. Based on inclusion and exclusion criteria 100 patients with epilepsy and 50 healthy age and sex matched subjects were recruited for the study.

The present study showed that 99 respondents out of 150 had the age below 20 years. The age and sex distributed homogenously between the two groups. In the study subjects' male were about twice than that of female.

The clinical presentations of the study patients were observed in the study. Generalized tonic-clonic convulsion was the major (79%) form of presentation in patients with epilepsy. About one-third Patients (36%) presented clinically with urinary incontinence. The study done by Jerome Engel [9] found 32.3% of patients with urinary incontinence. About one-third patients (35%) presented clinically with tongue bite. Benbadis [10] found 34 epileptic patients out of 106 had tongue bite. A little over one-third patients (39%) presented clinically with froothy sputum. About one fourth of the study subjects presented with the history of involuntary movement of limbs.

In this study 17% patients had the complaints of screaming. Fourteen percent subjects in the study presented clinically with sudden fall. Sudden anxiousness and frightening was the presenting feature in 9% of the study subjects. Only 6% of the patients had the symptom of spontaneous activity.

Myoclonic jerk (2%) was a rare form of clinical presentation in the study subjects. The difference of percentage of these clinical presentations were statistically significant ($p<0.001$). This finding is consistant with findings of several other studies [9-11].

Sensitivity is the proportion of patients with disease that have an abnormal test. In our study this is the proportion of patients with epilepsies who had an abnormal EEG. This is expressed as the number of patients with epileptiform discharges divided by the number of patients with the epilepsy. In the present study, the sensitivity of EEG in diagnosis of epilepsy was 74%. The study conducted by Gegory shows that interictal epileptiform discharges are demonstrated on 29% to 55% of patients with the clinical diagnosis of epilepsy [12].

Positive predictive value (PPV) of the test is the percentage of positive test that have the disease and the negative predictive value (NPV) is the percentage of negative test that have no disease. The positive predictive value of any test is the likelihood that a patient with a positive test will have the disease. In the present study, the chance that a patient with epileptiform discharges on EEG will have epilepsy. The PPV and NPV of EEG in the study were 96% and 62.7%.

The study by Nathan et al. found that the sensitivity of routine EEG after a single seizure is only about 30% and the PPV is >80% [13]. In contrast, Sam et al. found that 64 (12%) out of 521 non-epileptic subjects had interictal epileptiform discharges on routine EEG's performed as a part of neurological evaluation [14].

The specificity of the method or test is the percentage of true negative case; among the healthy group. In the study, the specificity of the EEG was 94%. Nazar et

al found the 61% specificity of EEG of the patient referred to the neurology department of neurology from the various health centers of Peshwar, Pakistan[15]. The combined power of the diagnostic efficiency of the test is the accuracy. Meta analysis of 25 studies[2, 6, 16] involving EEG by Donald et al, found that specificity (range 0.13-.099) and sensitivity (0.20-0.91) of epileptiform EEG varied widely and was heterogeneous by chi-square analysis. The accuracy of EEG diagnosis accounted for 37% [17].

The accuracy of the EEG in this study was 80.6%. The higher accuracy in our present study might be due to smaller sample size of our study; also it is not a multi centre study and it is done in tertiary level hospital. The differentiation was statistically significant (P<0.05) in EEG findings and clinical diagnosis.

Conclusion

This study was carried out to compare the clinical diagnosis of epilepsy with interictal EEG. "Epilepsy clinic" of Dhaka Medical College was chosen for the study. Between July 2006 to June 2007, 100 patients and 50 controls were selected as per inclusion and exclusion criteria. Age and sex of the controls and cases were well matched. In this study patients were broadly diagnosed as primary generalized epilepsy and localization related epilepsy on the basis of definite clinical parameter. They are further EEG classified as having generalized epileptiform discharge and focal epileptiform discharge and normal. The comparison of EEG findings and clinical diagnosis was statistically significant (P<0.05).

The present study has a very small sample size of only 100 epileptic patients and it was done on a tertiary level hospital. Most of the patients attending the tertiary level hospital already have several unprovoked seizures so as a diagnostic tool EEG has a high sensitivity, specificity as well as accuracy in this study. In contrast Meta analysis of large sample multicentre community based studies revealed EEG as a diagnostic tool as very low accuracy. To get better result large sample size should have been taken. Physicians should emphasize on clinical history in the diagnosis of epilepsy and perform EEG as supportive evidence when diagnosis is in doubt. In our perspective at least district level hospital should be equipped with efficient neurologists and EEG service is to be provided.

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CASE REPORTS

A Boy with Typical Presentation of MELAS

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Abstract:

MELAS is the most common mitochondrial encephalomyopathy. The onset in the majority of patients is before 20 years of age. MELAS is caused by maternally inherited point mutations of mitochondrial tRNA genes. The A3243G point mutation in $tRNA^{Leu(UUR)}$ is the most common, occurring in 80% of MELAS cases. The typical presentation of patients with MELAS syndrome includes features that comprise the name of the disorders, such as mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes. Other features, such as seizures, diabetes mellitus, hearing loss, cardiac disease, short stature, endocrinopathies, exercise intolerance, and neuropsychiatric dysfunction are clearly part of the disorder. We are reporting a 14 year old right handed boy presented at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka on 22nd May, 2008. The present work highlights the classic mode of presentation of MELAS and how lack of strong suspicion leads to dilemma in diagnosis of the disease. We also highlighted the lack of facilities for confirming the diagnosis of MELAS in our country.

Introduction:

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes – abbreviated to MELAS – is one of the family of mitochondrial cytopathies, caused by defects in the mitochondrial genome which is inherited purely from the female parent. It is a progressive neurodegenerative disorder, can manifest in both sexes equally. This condition affects many of the body's systems, particularly the brain (encephalo-) and muscles (myopathy). In most cases, the signs and symptoms of this disorder appear in childhood (4-15 years) following a period of normal development[1]. Early symptoms may include muscle weakness and pain, recurrent migraine like headaches, loss of appetite, vomiting, and seizures[2].Most affected individuals experience stroke-like episodes beginning before age 40 and as early as the teens[3]. These episodes often manifest as temporary hemiparesis, altered consciousness, vision abnormalities, seizures, and severe headaches resembling migraine. Repeated stroke-like episodes can progressively damage the brain, leading to vision loss, problems with movement, and a loss of intellectual function (dementia). In most patients with MELAS have lactic acidosis which leads to vomiting, abdominal pain, extreme tiredness (fatigue), muscle weakness, loss of bowel control, and difficulty in breathing. Less

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commonly, people with MELAS may experience involuntary muscle spasms (myoclonus), impaired muscle coordination (ataxia), hearing loss, heart and kidney problems, diabetes, epilepsy, and hormonal imbalances[2]. Other abnormalities that may be observed are ventricular dilatation, cortical atrophy, and basal ganglia calcification. Mental deterioration usually progresses after repeated episodic attacks. Psychiatric abnormalities and cognitive decline (e.g, altered mental status, schizophrenia) may accompany the stroke like episodes. Bipolar disorder is another psychiatric abnormality observed in MELAS syndrome. Autism spectrum disorders (ASDs) can be early presentations. Myopathy may be debilitating. Another cause of high mortality is the less common feature of cardiac involvement, which can include hypertrophic cardiomyopathy, hypertension, and conduction abnormalities, such as atrioventricular blocks, long QT syndrome, or Wolff-Parkinson-White syndrome[4]. Patients may develop renal failure due to focal segmental glomerulosclerosis. Severe gastrointestinal dysmotility and skin manifestations of cutaneous purpura, hirsutism, and a scaly, pruritic, diffuse erythema with reticular pigmentation may be observed in patients with MELAS syndrome. Short stature may be the first manifestation in many patients[5]. Hypothalamic pituitary dysfunction causing growth hormone deficiency, hypothyroidism, hyperthyroidism and absence of secondary sexual characteristics are rare presentations[6]. If the history and physical findings are suggestive of MELAS, lactice acid and pyruvate may be used as screening tests. Other tests include CSF lactic acid, CSF pyruvic acid, blood sugar, ECG, Echocardiographty, EEG, Neuro-imaging (CT, MRI or MRS scan of brain), histological examination of biopsied muscle and mitochondrial DNA analysis. Characteristics of lactic acidosis in MELAS are somewhat unique.

Arterial lactate and pyruvate are high and cerebrospinal fluid (CSF) lactate also may be high. Lactate and pyruvate may increase substantially with exercise.

Lactate/pyruvate ratio may be increased.The increased lactate/pyruvate ratio is observed in the face of a normal O_2 saturation, as opposed to tissue-injury lactic acidosis in which the increased ratio is associated with decreased O_2 saturation.

Case history:

A 14 year old right handed boy from Sylhet, Bangladesh admitted in neurology department of BSMMU, Dhaka, Bangladesh on 22nd May 2008, with the complains of sudden onset of blurring of vision and lightheadedness for 6 days, frequent episodes of headache and vomiting for last 3 months.

On detailed history from his brother we came to know that he has a normal birth history and normal early milestones of development. He had a poor health and appetite from his early life, managed to start education but dropped out at class V due to inattentiveness and restlessness. He used to be tired after minimum exertion. He became hot tampered. At about the middle of February 2008, he suffered a bout of headache which was severe in intensity, continuous and was not associated with fever, vomiting, convulsion or unconsciousness and did not subside after

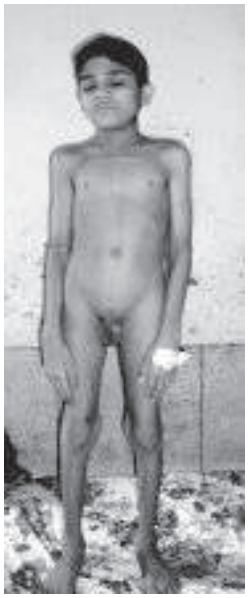

Fig.-1: *patient with generalized wasting and loss of development of secondary sexual characters*

taking paracetamol. His appetite further worsened. After about a week headache was accompanied by vomiting which gradually increases in frequency and became projectile. The vomiting did not relieved headache. About a week later they consult with a local gastroenterologist who advised him to admit in hospital. Then he was treated in pediatric department of a tertiary level hospital and on 8th day of admission in hospital he developed chicken pox and hospital authority discharged him on 29.03.2008 leveling as a case of ischemic stroke with left sided hemiparesis and bilateral basal ganglia calcification.

Some sort of improvement of headache was noticed at that time. For further improvement they consult a local neurologist and admitted on 08th April 2008 in the same tertiary hospital in neurology

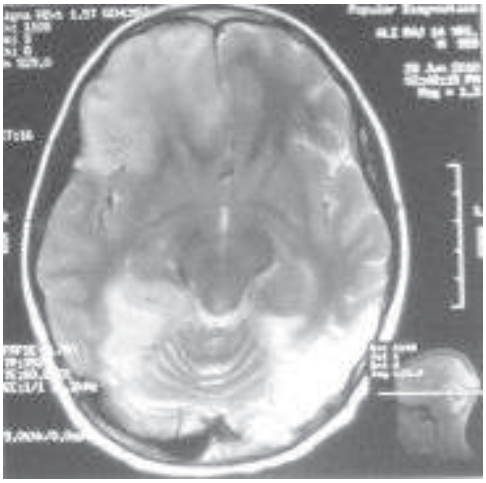

Fig.2: *CT scan head showing left parieto-occipital, bilateral frontal and right parietal infarction with bilateral diffuse basal ganglia calcification.*

department. He was treated conservatively and discharged as a case of ischemic stroke. At the time of discharge he was symptomless. After a daylong exertion in a social festival on 17.06.2008 he again developed an episode of headache, restlessness and tiredness at 9:00pm and partially relieved after taking rest. On following night he vomited 3 times and next morning after waking form sleep he lost his vision. They consulted with the neurologist who examined him and found no abnormality and referred him to a psychiatrist. After psychiatric evaluation he found no psychological abnormality and referred to one of our co-author who admitted the patient in neurology ward of BSMMU. In neurology ward he was underwent thorough physical examination which yielded the following findings:

On general examination the patient was found ill looking, emaciated, myopathic faces, short statured (4'1"), low weight

(20kg), moderately anemic, pulse 90/min, BP-90/60 mm of Hg. Examination of genitourinary system reveals no growth of secondary sexual character, testes and penis were infantile in size. Examination of cardiovascular system revealed no obvious abnormality. Respiratory and gastrointestinal system examination revealed no abnormality. On neurological examination his higher mental function shows poor intelligence; but speech normal; cranial nerves examination shows bilateral optic nerve lesion(pupil dilated, reactive to light, visual acuity reduced to hand movement, loss of colour vision, early optic atrophy), mild sensorineural hearing loss. Examination of motor system revealed bulk and tone were reduced in all 4 limbs, muscle power was 4+ in right side and 4- in left side, deep tendon reflexes were diminished in upper limbs and normal in lower limbs, plantar responses were flexor bilaterally co-ordination and gait was found normal. Examination of sensory system was normal. The laboratory investigation reports are summarized below:

Urine R/M/E showed protein-trace, Pus cell 2-6/HPF; TC of WBC was 8500/cmm; DC of WBC were Neutrophil-75%, Lymphocyte-20%, Monocyte-02%, Eosinophil-03%; Haemoglobin was 11 gm/dl; ESR was 49 mm in 1st hour;

Random blood sugar was 6.3 mmol/L; S. creatinine was 0.4 mg/dl; Inorganic phosphate was 4.3mg/dl; S. calcium was 8.1 mg/dl; Serum albumin was 45 gm/dl; Serum lactate was 79.50 mg/dl(normal range); Serum PTH was 10.1 pgm/ml; Serum TSH was 1.67 mIU/L; Serum FT_4 was 15.45 mIU/L; Serum growth hormone was 1.2 ngm/ml; Serum testosterone was 0.04ngm/ml (Normal value for his age, 0.1-0.2ngm/ml); Serum total cholesterol was 219mg/dl, HDL 50 mg/dl; LDL 131 mg/dl and triglycerides 183 mg/dl. EEG features were suggestive of encephalopathy; EMG features were suggestive of myopathy; ECG showed sinus tachycardia but

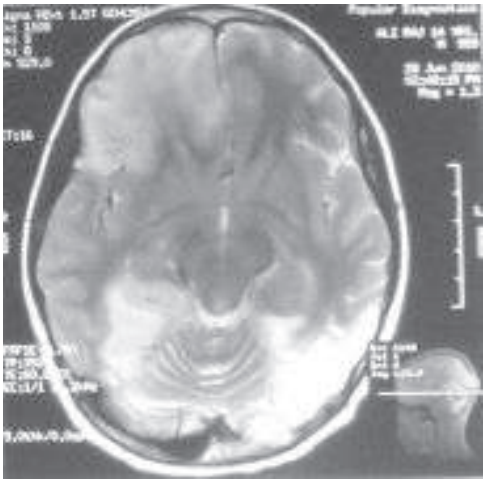

Fig.3: *T_1 weighted MRI shows bilateral cerebral ischemic changes of different ages/right sided encephalitis with chronic ischemic changes in left occipital region.*

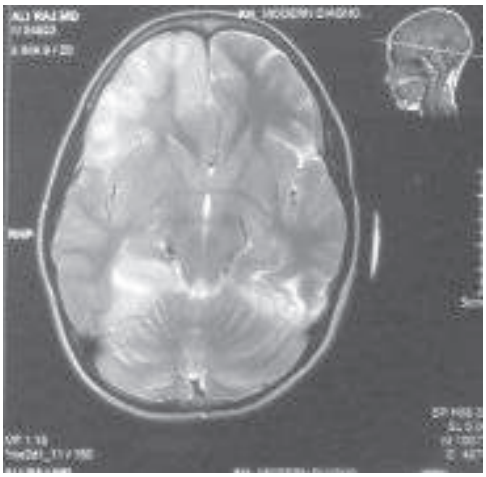

Fig.4: *T_2 weighted MRI showing similar changes as found in TW_1 MRI*

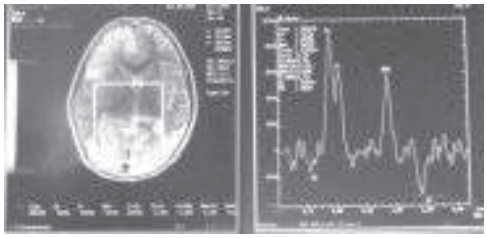

Fig.-5: *MRS showing lactate pick.*

echocardiography was normal. USG of abdomen was normal; CT scan of brain showed left sided massive cerebral infarct and bilateral basal ganglia calcifications (Fig.-2); MRI of brain (Fig.-3,4) showed a) bilateral cerebral ischemic changes of different ages/right sided encephalitis with chronic ischemic changes in left occipital region. b) metabolic encephalopathy. MRS showed recent/ subacute infarct in right frontal and right occipito-parietal lobes, old infarct in left occipito-parietal lobes and there are multiple lipid-lactate peaks are seen, suggesting infarct/hypoxia (Fig.-5).

Discussion:

Diagnosis of MELAS is based on clinical presentation, family history of such illness and laboratory investigations. Mitochondrial DNA analysis is now available commercially from several sources to identify the mutations responsible for this disease. CT scan of the head may demonstrate areas of low attenuation that do not correspond to vascular territories and that may be transient, predominantly in the temporoparietal and occipital cortices and subjacent white matter. Basal ganglia calcification and generalized atrophy also are seen. MRI studies show hyperintense T2 lesions predominantly in the gray and subcortical white matter in the temporal, parietal, and occipital lobes. Basal ganglia calcifications and atrophy also are reported. Generalized cerebral atrophy is frequent[7]. By using MR spectroscopy, several groups have shown that lactic acid levels in the brain parenchyma and ventricles may be increased during the acute phase of the disease and in chronic lesions[8,9]. Findings of noninvasive and cerebral angiographic studies are generally normal or show focal capillary blush or early venous filling in affected cortical regions. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) studies have been reported variably to show normal or increased (and occasionally diminished) cerebral blood flow to regions structurally abnormal on CT scan and MRI[10]. Metabolic PET studies demonstrate focally deranged metabolic states. EEG is often performed when seizures are a concern. Electrocardiogram may reveal preexcitation or incomplete heart block. Echocardiogram may demonstrate cardiomyopathy. If MELAS syndrome is suspected and if the mtDNA mutation analysis in blood and other accessible tissues provide unremarkable results, a muscle biopsy should be performed. In muscle biopsies stained with hematoxylin and eosin, variation is observed in type 1 and type 2 fiber sizes, representing myopathic changes. Ragged red fibers are the hallmark of MELAS syndrome.

Our patient is a sporadic case. Typically presented with migraine-like repeated headache, vomiting, recurrent stroke-like episodes, cortical blindness and severe generalized weakness. On physical examination he was found ill-looking, emaciated, myopathic faces, short statured, mildly anemic, normotensive, had no secondary sexual character with

infantile testes and penis. Nervous system examination revealed early optic atrophy, reduced visual acuity with loss of colour vision, mild sensorineural hearing loss; reduced muscle bulk, tone and power with normal coordination and sensation. Investigations showed haemoglobin 11gm/dl, ESR 49 mm in 1st hour, serum lactate 79.50mg/dl (markedly increased), serum testosterone 0.04ngm/ml (markedly reduced). EEG showed features suggestive of encephalopathy. CT scan of brain showed left sided massive cerebral infarct and bilateral basal ganglia calcifications, MRI of brain showed-a) bilateral cerebral ischemic changes of different ages/right sided encephalitis with chronic ischemic changes in left occipital region, b) metabolic encephalopathy; MRS revealed multiple lipid-lactated peaks , suggestive of infarct/hypoxia.

All the clinical features and laboratory findings are suggestive of MELAS but for confirmation of the diagnosis we needed muscle biopsy with Gomri stain or cytochrome oxidase stain but in Bangladesh these facilities were not available. We had another tool for confirmation of diagnosis, which was genetic analysis for detection of mutation in 3243 location of mitochondrial genome which was also lacking here.

There is no known treatment for the underlying disease. Patients are managed according to what areas of the body are affected at a particular time. Enzymes, amino acids, antioxidants and vitamins have been used, but there have been no consistent successes reported. The effect of dietary manipulation is not completely known, and the efficacy of dietary supplements is unproven. Improvement observed in many patients is probably related to improved nutrition. The following supplements have shown promise and given hope to MELAS patients. CoQ10 has been helpful for some MELAS patients[11]. Nicotinamide has been used because complex I accepts electrons from NADH and ultimately transfers electrons to CoQ10. Riboflavin has been reported to improve the function of a patient with complex I deficiency and the 3250T-C mutation[12]. The administration of L-arginine during the acute and interictal periods may represent a potential new therapy for this syndrome to reduce brain damage due to impaired vasodilation in intracerebral arteries owing to nitric oxide depletion[13,14]. Both intravenous and oral formulations of dichloroacetate have been used in the acute treatment of stroke-like episodes, as well as in long-term prophylaxis of stroke in patients with MELAS. The possible therapeutic effect of dichloroacetate was thought to be mediated via reduction in lactate levels in blood and brain[15,16]. Cardiochrome, a combination of cytochrome c and vitamins B1 and B2, may increase the effectiveness of the electron transport chain of the inner mitochondrial membrane[17]. L-arginine showed improved flow-mediated vasodilatory response[18].

We have treated our patient with riboflavin mg PO 8 hourly, ascorbic acid 250mg PO 8 hourly as he could not tolerate higher doses due to gastrointestinal disturbances; L-carnitine 330mg 8hourly, Nicotinamide 50mg 12hourly. We discharged him on request. After about a week later he developed focal seizure with secondary generalization. After two episodes of such attack they noticed us about the seizure

and we gave him carbamazepine 200mg PO 12hourly and no more seizure attack occurred.

Conclusion:

MELAS is a progressive and ultimately fatal neurological disorder, with a tendency to relapses and remissions. At present no curative treatment is available. It is a under diagnosed disorder. Any patient suffering from ischaemic stroke before the age of 40 should be suspected for this disorder.

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Intracranial Extradural Hydatid Cyst : A Case Report

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Abstract

Hydatid disease occurs in humans as a result of faeco-oral contamination. It is caused by the infestation of the larvae of Echinocccus granulosus. Hydatid disease of the Central Nervous System (CNS) is very rare and accounts for 0.2-4 % of all hydatid cases, intracranial extradural hydatid cyst is even rarer. Only 18 cases of intracranial extradural hydatid cyst have been reported till 2000. We are reporting a case of this rare entity of the isolated intracranial extradural hydatid cysts in a 21 year old young man, who presented with history of headache and visual disturbance. The patient underwent craniotomy with total excision of the cysts. The diagnosis of the hydatid disease was confirmed on histopathology. Patient was given albendazole for 3 months postoperatively. Three months after the surgery, CT scan here showed no evidence of residual cyst or recurrence and the patient was doing well. We are presenting the case hre for its rarity and to the best of our knowledge it is the first reported case in Bangladesh.

Key Words : *Hydatid, Echinocccus granulosus, Intracranial extradural hydatid cyst, Albendazole.*

Introduction

Echinococosis or hydatid disease is caused by larvae of *Echinococcus granulosus* and related species, which are small tapeworms found primarily in dogs and is the most widespread, serious human cestode infection in the world. The disease is more common endemically where sheep and cattle are more common, including South America, the Middle East, some Mediterranean countries, Middle Asia, Australia and East Africa[1-6]. Humans are generally an incidental intermediate host, infected by the parasite frequently through the ingestion of the ova and rarely by inhalation. Embryo becomes free after the digestion of ova in the gastrointestinal tract, and the resultant embryo most often settles in the liver through portal circulation. Some may reach the lungs and occasionally, some may pass through the capillary filter of the liver and lungs and get entry into the systemic circulation and may involve various organs, where it can cause hydatid disease. These may even reach the brain[1,5,7]. The most common sites of infestation are the liver (75%) and lungs (15%) and only 10% occur in the rest of the body. Various authours state a frequency of hydatidosis of the brain ranging between only 0.2-4% of cases[2-4,8-11]. An intracranial extradural

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hydatid cyst is a very rare occurrence with unclear pathogenesis. Only 12 cases till 1996 and 18 cases till 2000 have been reported previously in the literature[12-14].

Case Report

A 27 year old young man was admitted in the neurosurgery department of Bangabandhu Sheikh Mujib Medical University with the complaints of headache for one year. The headache was in the frontal region, aching in nature, usually in the morning, sometimes was associated with vomiting. He also complained of pain in both eyeballs, more on the right side. Initially it used to persist for few hours and occurred every 2-3 months. On admission, the pain was constant and used to be relieved to some extent by pain killers and vomiting. He gave no history of visual impairment, loss of consciousness, convulsion or weakness of any limb. He did not have any history of fever, cough, haemoptysis, ear infection, anorexia or weight loss. No history of having any pet animal or rearing any cattle or eating raw meat was elicited. On physical examination he was a man of average built with vital parameters within normal limit. There was a swelling in the left frontal region which was about 2cm×2cm, had ill defined margin and bony hard in consistency. Respiratory and abdominal examinations revealed no abnormality. He was neurologically intact. On investigation, his CBC was within normal limit. X-ray skull showed a small lytic area in the left frontal region. X-ray chest was normal. Ultrasound scan of abdomen was normal. MRI images were suggestive of an arachnoid cyst in the frontal region (Fig.-1).

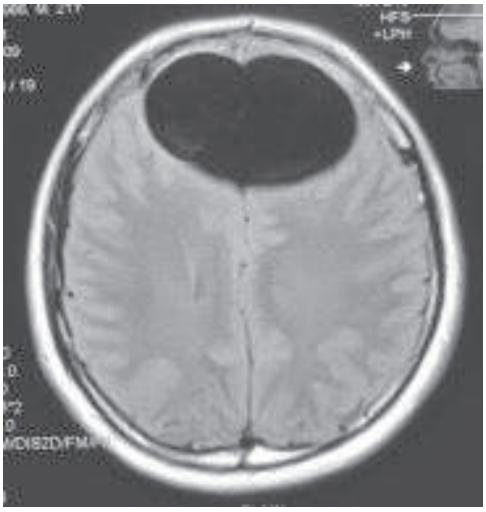

Fig.-1*: T1WI of MRI showing cystic space occupying the both frontal regions, suggestive of an arachnoid cyst.*

A left frontal craniotomy was done. On removal of the bone small amount of clear fluid came out and we thought that we have punctured the dura. Later on after careful inspection it was found that there were two big extradural cystic lesions with thin wall, one of which was punctured accidentally during craniotomy and a few smaller ones inside the bone invading it, scalloping the bone, highly suspicious of hydatid cysts (Fig.-2).

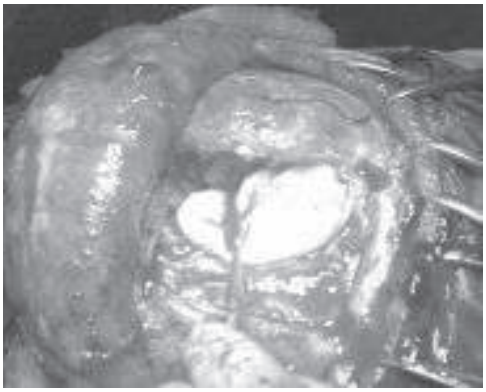

Fig.-2: *Peroperative picture showing one of the two big extradural cystic lesions with thin wall and a few smaller ones inside the bone*

All the extradural cysts were removed intact, except one of the large ones which was nicked initially during craniotomy, with saline irrigation and meticulous dissection. The cysts embedded in the bone were shelled out intact. Thorough saline irrigation was applied. Histopathology confirmed that they were hydatid cysts. Post-operatively ICT for Echinococcus was found positive. We discharged the patient with Albendazole 400 mg twice daily for 3 months. During follow up at three months, the patient was doing well and his CT scan of brain showed no evidence of residual or recurrent cyst (Fig.-3).

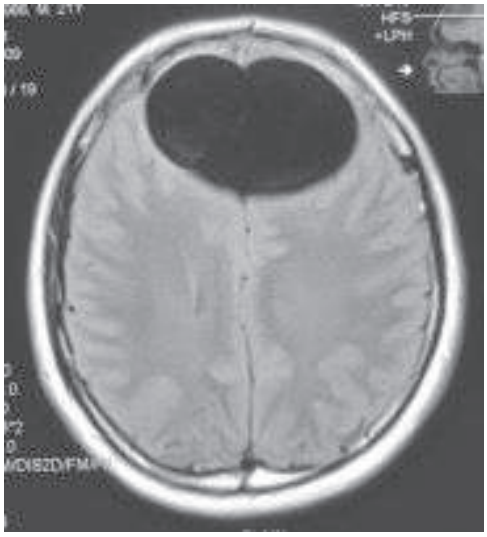

Fig.-3: *Post-operative contrast enhanced CT scan showing no residual cyst or recurrence*

Discussion

Echinococcosis is one of the earliest known parasitic infestations of human. The occurrence of the disease in man is related to the areas where close contact exists between domesticated carnivores and infected cattle and sheep. The history of direct contact with dogs is not available in all the cases, as the infection can be acquired by eating contaminated food and milk[15,16]. Man is an accidental intermediate host. About 2-4% of cases of hydatid disease involve the central nervous system [2-4,8-11,15-16].

Intracranial hydatid cysts are classified as primary or secondary depending on whether other organs have been involved or not. The primary cysts are formed as a result of direct infestation of the larvae in the brain without demonstrable involvement of other organs. In primary, multiple cysts; each cyst has a separate pericyst with brood capsule scolices and these originate from multiple larvae affecting brain after crossing the gastrointestinal tract, liver, lungs and right side of heart without affecting them and their rupture can produce secondary cysts which lack scolices and brood capsules. Primary multiple cysts are rare. Most cysts being secondary resulting from spontaneous, traumatic or surgical rupture of the primary intracranial hydatid cyst. As they lack brood capsule and scolices, the secondary intracranial hydatid cysts are therefore, infertile and the resultant risk of recurrence after their rupture is negligible[1,2,16]. In the present case it seems that the patient had primary multiple cysts as presence of hydatid disease was not evident elsewhere in the body. Though there were multiple cysts, it was not clear whether those were separate pericysts with brood capsule. But as the patient had no history of trauma or surgery previously it is most likely that the cysts were primary ones. Primary intracranial extracerebral hydatid cysts have been reported but are extremely rare. They occur in three forms:

1) Cranial—usually the osseous spongiosa is the first to be involved, with only 2% of the hydatid cysts localized to the skeleton and only 3-4% of these are in the skull; 2) Cranial extradural-the extradural space may be infected by embolization of scolices or embryos via blood vessels, by extrusion of intracerebral cysts via healthy dura mater, or by erosion of osseous hydatid lesion into the extradural space; and 3) combined location- there may be simultaneous intracerebral, extradural, and osseous cysts. Of the three forms, extradural variety is extremely rare as the physiologic flow of blood to the brain is mainly through the internal carotid system, so the likelihood of the larvae travelling through the external carotid system is very low[2,5]. In case of our patient obviously these were extradural hydatid cysts. We feel that these are of pure cranial extradural type as there was no involvement of the skull bones. The cranium was scalloped from long standing pressure but did not erode the bone. (Fig.-4).

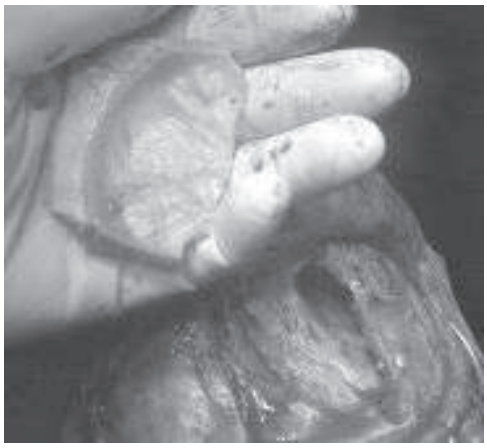

Fig.-4: *Peroperative picture showing scalloping of the frontal bone from long standing pressure, but not eroding the bone.*

Intracranial hydatid cysts are more frequently located in the supratentorial compartment, in middle cerebral artery territory, commonly in the parietal lobes[1,2,7,8,15]. The other less common sites reported are skull, cavernous sinus, eye balls, pons, extradural space, cerebellum, ventricles, meninges and brainstem[1,2,16]. Our patient had the cysts extradurally in the frontal region which is one of the rare sites and only 18 cases of intracranial extradural hydatid cyst have been reported in the literature till 2000. Children are more commonly affected than adults[2,8]. Though it is more common in children this was a case in a young adult. The cerebral hydatid cysts are slow growing and present late when they increase in size and are typically large, averaging 4–10 cm in diameter. Growth rate has been variably reported between 1.5-10 cm / year[1,2,7,16,17]. The two bigger cysts of our patient were of 3.5 x 4 cm and 4 x 5 cm respectively which are considered to be moderately large. As the patient had symptoms for one year it is likely that it grew slowly over years.

The signs and symptoms are those of a slowly growing tumour. The patients with intracranial hydatid cysts usually present with focal neurological deficit and features of raised intracranial pressure; the latter may be due to the large size or due to interference with pathway of the CSF flow. Patients may present with seizure. The disparity between the size of the cyst and physical signs is an important feature of cranial hydatid cysts[1,7,8,15,16]. In our case the signs and symptoms presented

typically like a slow growing space occupying lesion. He did not have any neurological deficit. The only complaint was headache and pain in the eye balls which seem to be from pressure and stretch on the dura. Despite of its moderately big size, absence of any neurological deficit implies that it was a very slow growing one.

MRI and CT scans characteristically show hydatid cyst as a spherical, well-defined, non-enhancing cystic lesion without peripheral oedema. The fluid density is generally equal to that of CSF on both CT and MRI scan. CSF density (on CT) or intensity (on MRI) lesions with a fine fibrous wall which on T2WI MR scans appears as hypointense ring; this appearance being considered diagnostic. A fine rim of peripheral enhancement with perilesional oedema may be seen in the presence of active inflammation. MRI scan may show a low density cyst wall and relations with surrounding structures are better delineated than on CT scan. Calcification is seen in less than one percent of cases and is better seen on CT. The scolices of the cyst are not seen on MRI[1,2,7,16,17]. MRI of our patient showed two big and a few small well defined spherical cystic lesions having the intensity like that of CSF without any perifocal oedema. They had fine hypointense septa in-between in T2WI which was smooth and regular at most parts. Only in some parts, especially around the smaller cysts they had irregular margins (Fig. 5 & 6).

We could not identify scolices on MRI scan. Other differentials apart from infective lesions and astrocytomas are epidermoid, arachnoid cyst, neurocysticercosis and porencephalic cyst. Arachnoid cyst has

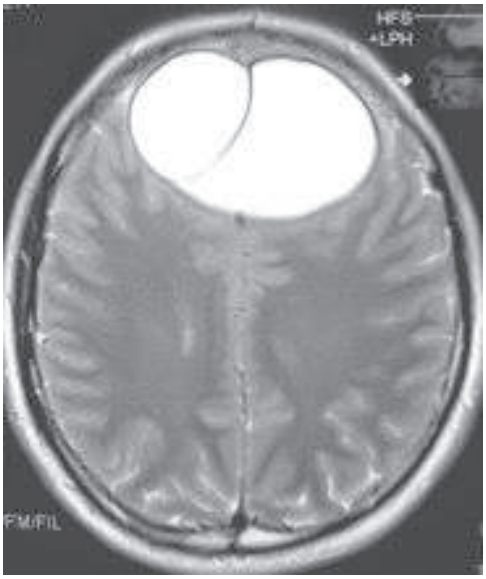

Fig.-5: *T2WI of MRI showing fine hypointense smooth and regular septa between two larger cysts at most parts*

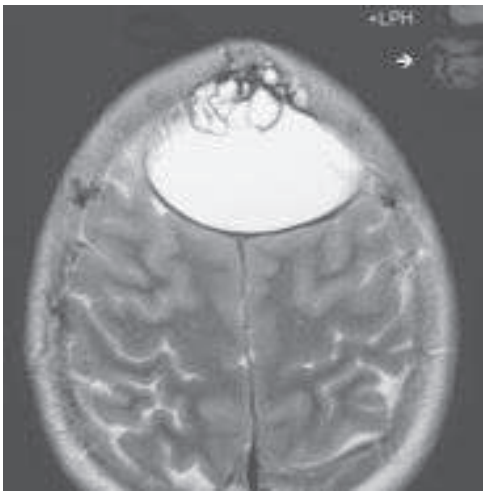

Fig.-6: *T2WI of MRI showing irregular septa between smaller cysts*

similar appearance as that of a hydatid but they are said to have an irregular inner border and are not spherical shaped[2]. As

the lesion had irregular margin at some places our initial thought was of an arachnoid cyst. But the spherical shape of the larger two cysts were not in favour of a typical arachnoid cyst. And later it was found per-operatively that these were not arachnoid cysts. Epidermoids can be differentiated usually by their lobulated, vessel engulfing, self moulding behaviour. However in certain situations diagnosis can be difficult[1,2,17]. Novel diagnostic methodologies such as MR spectroscopy and MR diffusion-weighted imaging might help in the diagnosis of intracranial hydatid cysts[16]. Kohli et al performed in vivo and in vitro MR spectroscopy (MRS) studies in a patient of intracranial hydatid cyst. Besides lactate, alanine and acetate, a large resonance for pyruvate was observed. MRS pattern appeared different from the other cystic lesions of brain and they suggested MRS as an adjunct to imaging in the differential diagnosis of intracranial hydatid. Role of MRS in monitoring drug therapy was also highlighted[18]. We did not do any MRS as we were not thinking of a hydatid cyst in the beginning. Echocardiography, and examinations of the chest and abdominal organs with radiography and ultrasonography, respectively, must be performed routinely to exclude hydatid disease of lung and liver. Histopathology confirms the presence of hydatid cysts, with germinal epithelium[5,19]. X-ray chest and ultrasonography of the abdomen did not reveal any trace of hydatid disease elsewhere. So, it is evident that this was a case of primary hydatid cyst. And histopathology confirmed the diagnisis. Serological tests (Casoni test), peripheral blood and cerebrospinal fluid eosinophilia, may be helpful for the diagnosis of hydatid disease. These tests may frequently yield negative findings[5,15]. ICT for Echinococcus was positive post-operatively – another confirmation of the lesion to be hydatid cyst, which is not positive always.

The treatment of hydatid cyst is essentially surgical and the aim of surgery is to excise the cyst in toto without rupture to prevent recurrence and anaphylactic reaction. The main factor governing prognosis is the intact removal of the complete cyst, which is a curative procedure and the outcome remains excellent in these cases. Correct preoperative diagnosis is vital for the successful outcome of the surgery. A high index of suspicion is therefore required in endemic areas despite the availability of advanced neuroimaging techniques[1,7,8,15,16,19]. We excised the cysts intact. During craniotomy discharge of some fluid initially gave us the suspicion that we might have punctured the dura. But later after the craniotomy we found one of the larger cysts was collapsed a little, which was punctured during craniotomy. The other large one and rest of the smaller cysts were shelled out intact. For intracerebral hydatid cysts various surgical options as puncture and aspiration of the cyst fluid through a small hole in the cyst wall, cortical incision over cyst and expulsion of hydatid cyst by insufflation of air in the contralateral ventricle and the most commonly done procedure designed to give birth to the intact cyst by irrigation of saline between cyst wall-brain interface. This is possible because of minimal adhesions around the cyst wall[1,16]. As the cysts were extradural and had no adhesion with the surrounding structures they came out without much difficulty by meticulous blunt dissection and copious saline irrigation.

Medical treatment with albendazole seems to be beneficial both pre- and postoperatively. Only a few reports are available that mention the efficacy of this drug therapy. Isolated case reports showed complete disappearance of the multiple intracranial hydatid cysts with albendazole therapy with a daily dose of 10 mg/kg, taken three times a day for 4 months[1,16]. Albendazole is a broad spectrum oral antihelminthic drug, which acts by blocking glucose uptake of the larvae and the adult worm. The glycogen storage is depleted and thereby decreasing the ATP formation resulting in the death of the parasite. On the other hand, by attacking the parasite's germinal layer, it causes degeneration of the layer which leads to a disturbance of homeostasis[1,6,7,16]. We put the patient on Albedazole 400 mg twice daily for 3 months and the patient was doing well after three months without any complication. Clinically he was doing well, returning to his daily activities and his follow up CT scan revealed no residual cyst or no evidence of recurrence at the end of follow up for 1 year.

Conclusion

Intracranial extradural hydatid cyst is a rare entity. Intact total removal followed by post-operative medical therapy with albendazole gives a good prognosis and reduces the chances of recurrence.

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Neuroendoscopic Treatment for Colloid Cyst of the Third Ventricle - Review of 5 Cases

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Abstract

Colloid cyst of the third ventricle is a relatively rare intracranial tumor. It generates tremendous interest for the neurosurgeon because of its benign nature, deep location, and an excellent prognosis when diagnosed early and excised.

However the treatment of this benign tumor remains controversial: and the best surgical option has not been established. Microsurgical resection or ventriculoperitoneal shunt placement was for a long time the only means of treatment for patients with colloid cysts. In the past few years, however, endoscopic procedures have gained increasing significance and have been used more widely. In BSMMU endoscopic treatment for colloid cyst was performed recently in five cases. The technique, consisting of cyst fenestration, aspiration of the colloid, and removal of the internal layer of the wall, was effective in restoring CSF circulation. In the early postoperative period, all the patients had excellent outcome, with clinical signs improving immediately. The analysis of immediate postoperative computed tomographic scan revealed no remaining cyst wall and decrease in ventricular size to some extent.

Continued improvement of endoscopic techniques and instruments, together with good short-term results in endoscopically treated patients, have established this method as an alternative to microsurgical techniques and might even set a new standard for treatment.

Introduction:

Colloid cysts are benign congenital tumours that almost always arise from the anterior third ventricle (immediately posterior to the foramen of Monro (Fig.-1)[1,2]. These epithelium-lined cysts are problematic because of their location; colloid cysts can cause serious morbidity and acute obstructive hydrocephalus that may lead to occasional mortality[2,3].

Approximately 0.5-1% of all primary brain tumours and 15-20% of all intraventricular masses the most common are colloid cysts[2]. The usual location of colloid cyst at the level of Foramen of Morno have led at least four theories of of pathogenesis.

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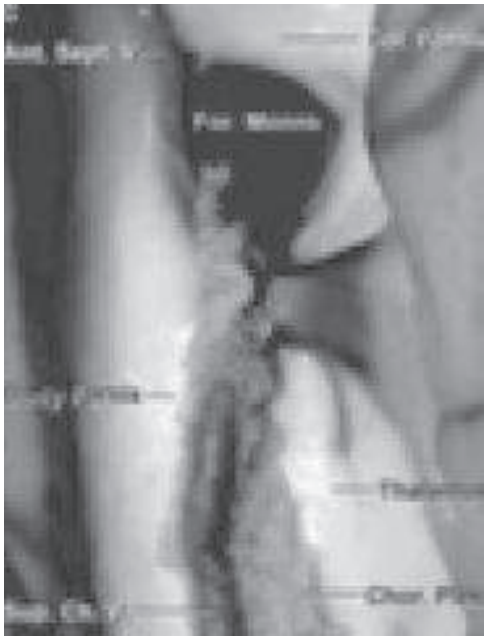

Fig.-1: *showing the foramen of Monro in relation with septal, thalamo-striate veins and choroids plexus.*

Derivation from choroidal epithelium, from ependymal cells, and from paraphysis have been described.In addition Hiron et al.-1978 suggest that colloid cysts arise from an endodermal source rather then neuroepithelial sources[2,3].

The colloid cysts were remnants of the paraphysis, an embryonic midline structure within the diencephalic roof immediately rostral to the telencephalic border. The cells of the paraphysis are similar to those found in colloid cyst[4,5] . Associated with falls without loss of consciousness has been reported[4,5.] Colloid cyst may obstruct the foramen of Monro completely and irreversibly, resulting in sudden loss of consciousness and, if patients are not treated, coma and subsequent death due to herniation[5,6]. This theory of death secondary to herniation has recently been challenged with an alternative theory that suggests that sudden death in patients with colloid cysts may be related to acute neurogenic cardiac dysfunction (secondary to acute hydrocephalus) and subsequent cardiac dysfunction, cardiac arrest rather than herniation[5-7].

The 3 approaches most commonly used for colloid cyst surgery[7], these are

1. Microneurosurgery - A.Transcortical approach, B. Interhemispheric transcallosal approach, 2. Endoscopic neurosurgery, 3. Steriotactic aspiration.

Materials and method:

In this study 5 patients recently underwent endoscopic removal of colloid cyst in BSMMU from July 2007 to September 2009.

The endoscopic approach was the same as the transcortical approach, except that the former is accomplished through a burr hole. The cyst is punctured and aspirated through the working channels of the endoscope. The basic requirements were –

GAAB universal neuroendoscopic system (Karl Storz Endoscope)

1. Operating sheath, 2. Rigid endosope with optics, 3. One working channel & two irrigation channels, 4. Puncture needle, 5. Grasping forceps, 6. Bipolar coagulation device.

Surgical Technique

The patient was placed in the supine position on the operating table. The neck was flexed approximately 30° to the horizontal plane and neutral in the vertical plane. The burr hole was placed 5 to 6 cm. from the midline and 11 cm. behind the nasion on the nondominant side (Fig.-2). Provisions should be made to convert the procedure into an open, transcortical approach if necessary. The lateral ventricle, free-hand needle ventricular puncture was performed before the endoscope was introduced. We did by a rigid 0° endoscope of 5-mm outer diameter for best optical clarity. Once anatomical landmarks and the tumor were identified, the cyst was punctured and the contents evacuated. When the cyst contains inspissated, firm material, cup forceps were required to remove the contents in a piecemeal fashion. Intermittent irrigation and bipolar cautery were done to keep the operative field clear.

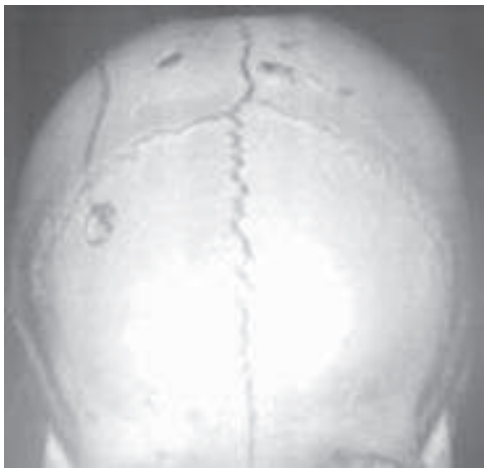

Fig.-2. *Shows the site of burr hole which was 5 cm lateral from the midline and 2 cm infront of coronal suture.*

Postoperative Management

Ventricular catheter was placed intraoperatively to safeguard against ventricular dilatation. It remained clamped & was removed on 3rd Post-opoerative day (POD).

Injection Methyl Prednisolone 500mg daily for 5 days to prevent chemical meningitis was given.

Result:

In Table-I summary of the age, sex, presenting symptoms, imaging findings and operative outcome was discussed. Age range was from 12-55 years (mean 32.4 year). All patients were presented with headache. All the 5 cases had moderate to severe hydrocephalus. All patients underwent endoscopic colloid cyst removal. All had uneventfully recovery except 1 patient (20%) had Pyogenic meningitis. One patient (20%) developed recurrence after 1 year for which he underwent exploration by transcranial transcallosal transventricular approach.

Endoscopic gross total removal of colloid cyst were done in 2 cases (40%)(Fig.3), subtotal in 2 cases (40%) (Fig-4) and only 1 case (10%) partial resection had to be done because of dense adhesion with internal cerebral veins.

All the tumour biopsy revealed cuboidal epithelial lined tissue supported by fibrous connective tissue suggestive of colloid cysts. (Fig. 5)

Table-I

Summary of cases, presenting symptoms, radiographic findings and outcome.

Case no	Age/ sex	Symptoms	hydrocep halus	Tumour size (cm)	Complic- ations	Follow up	Extent of resection
1.	35/M	Headache 6months ,no visual problem	+ +	4 cm	NIL	16 months no recurrence	Total
2.	12/M	Headache months, vomiting , Diplopia,	+ + +	5cm	Pyogenic meningitis	Recurrence after 1 year	Subtotal
3.	25/M	Headache- 1 year.	++	3 cm	NIL	1 year, no recurrence	Total
4.	55/M	Sudden headache vomiting , hemiparesis	+ +	4 cm	Nil	10 months no recurence	Subtotal
5.	35/M	Headache	+	4 cm	Peroperative bleeding	3 months no recurrence	Partial

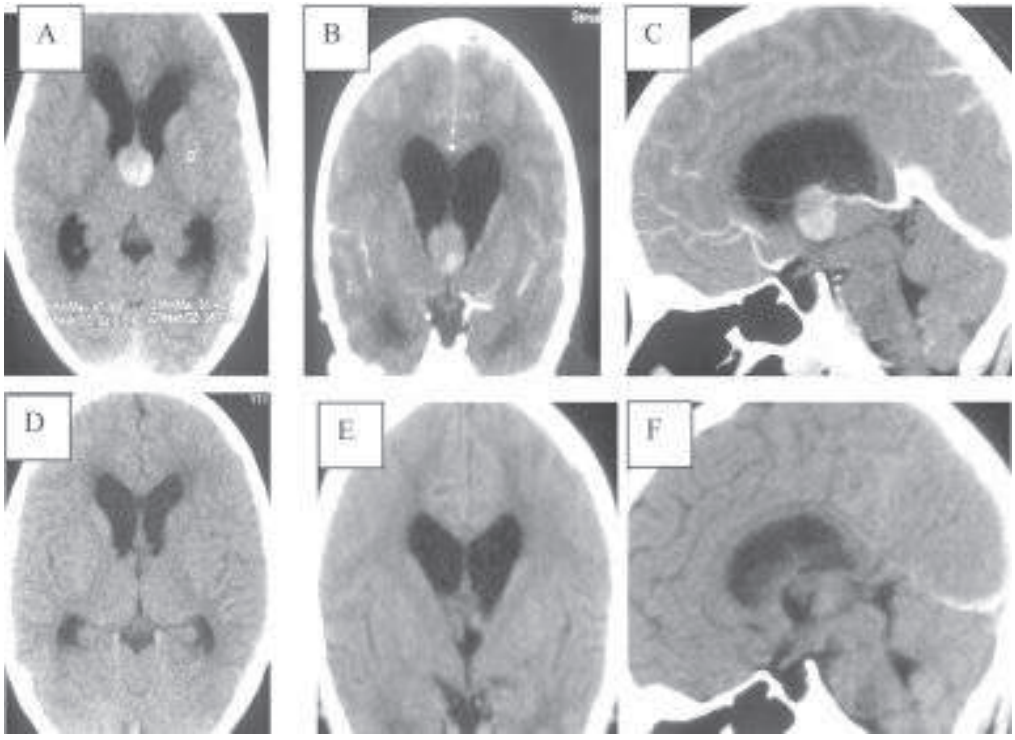

Fig.-3: *Preoperative and postoperative CT imaging of the patient, A.B, C, revealed axial, coronal and sagittal CT scan shows hyperdense mass in the anterior 3rd ventricle. D, E, F, Postoperative CT shows no residual colloid cyst and establishment of CSF pathway.*

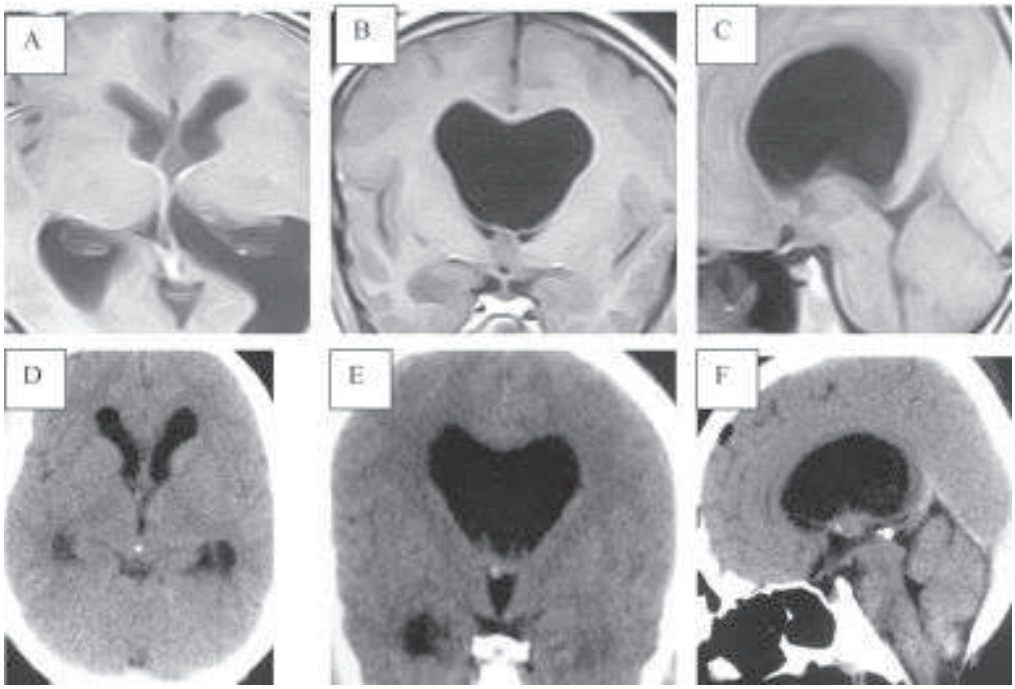

Fig.-4: *Preoperative MRI and postoperative CT scan of patient. A,B,C revealed axial, coronal and sagittal isointense colloid cyst . Postoperative CT image D, E F revealed very small remnant in the 3rd ventricle, CSF pathway has been reestablished.*

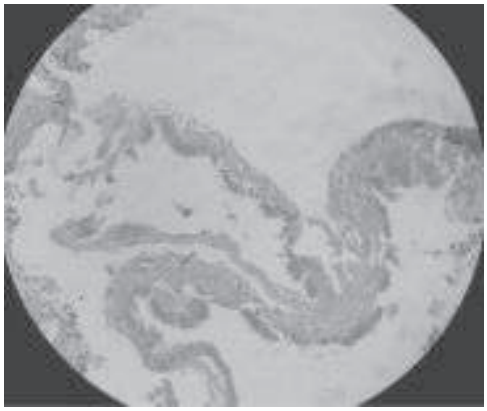

Fig.-4: *Histopathology of colloid cyst.*

Discussion:

Neuroimaging Studies-

CT scan of Head -

Colloid cysts appear homogenous, with two thirds of them appearing hyperdense to the surrounding parenchyma and one third appearing isodense to the surrounding parenchyma. The lesions are well delineated and are usually round or ovoid. Occasionally, the lesions have a thin rim of enhancement after contrast injection, but they are typically nonenhancing and are not calcified. The size of these cysts varies, but most are 5-25 mm[7,8] (Fig-2).

The CT scan is an important preoperative study because the viscosity of the cyst contents correlates more closely to the radiodensity visible on a CT scan than to the density visible on MRI. The viscosity of cyst contents determines the most appropriate surgical approach. A hyperdense cyst is more likely to have solid contents and is more difficult to drain. Hyperdensity may also correlate with a reduced capacity to enlarge over time[7,8].

MRI of brain

The appearances of colloid cysts on MRIs are variable. The most common appearance is hyperintensity on T1 and hypointensity on T2. The amount of rim enhancement is variable. The variable MRI signals do not correlate with the fluid density of cyst contents, although a MRI is valuable in differentiating a colloid cyst from a basilar tip aneurysm, which may have a similar appearance on a CT scan[8] (Fig-3).

Surgical management

In 1983 Powell, et al. [8] were the first to suggest endoscopic removal of colloid cysts. This was followed by several cases confirming the ability to remove colloid cysts successfully. In 1994 Lewis, et al., [9,10] published a series in which they compared endoscopic and microsurgical procedures for the removal of cysts, concluding that endoscopy was superior in terms of operative time and postoperative recovery. Since then, many other studies have reinforced the advantages of the endoscopic technique.

The Advantages are

1. Less damage of brain tissue.
2. Excellent view of intraventricular anatomy.
3. Assessment of relation of lesion to surrounding structures.

Each approach has specific risks and complications. The transcortical approach carries an increased incidence of epilepsy[11,12]. The transcallosal approach decreases the risk of postoperative epilepsy but risks of infarction and contralateral leg weakness from prolonged retraction. An extensive callosal resection may also cause temporary mutism[13,14]. Excessive manipulation of the fornix may affect memory. The endoscopic approach is the least invasive, but it can be used only on cysts that can be aspirated. Large cysts can not be removed with this technique. A steeper learning curve exists with the endoscopic technique[15].

Hydrocephalus can persist after surgery, even after resection of the cyst. This complication may be secondary to spillage of the cyst contents or to bleeding during surgery. A ventricular catheter may be placed intraoperatively to safeguard against ventricular dilatation[15].

In our study there were only one recurrence in 2 years follow up period in a young child. Following recurrence he underwent transcranial transcallosal approach and resection of recurrent colloid cyst without any postoperative complications.

Conclusion:

Colloid cysts of the third ventricle represent 0.5-2% of all intracranial tumours. The endoscopic approach for the removal of colloid cysts of the third ventricle represents a safe procedure, and can be considered a very good option for the treatment of these rare lesions.

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Intracranial Meningioma in a Twelve Year Old Boy with Haemophilia - A Case Report

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Abstract:

A 12-year-old boy with haemophilia who had a successful surgical resection of intracranial meningioma resulting in improvement of his symptom was reported. Surgical intervention was required because of clinical worsening in the form of medically refractory epilepsy. Fresh frozen plasma (FFP) was used before, during and after the procedure. Post-operatively patient developed hemiparesis due haemorrhage within the tumor bed but improved gradually as FFP was continued. subsequently the patient was seizure free. Neurosurgical interventions may be considered in haemophilic patients in special cases, as the one presented here.

Key words: *Meningioma, Fresh Frozen Plasma*

Introduction:

Haemophilia was the first hemorrhagic disorder to be accurately described when it was recognized as an hereditary bleeding disorder of males which is transmitted by healthy women[1]. In haemophilia A the level of factor VIII is reduced but the level of factor vWF is normal[2] . The frequency of haemophilia varies in different races; the highest incidence was reported in population of British and North European enciestry[1].

Meningiomas are rare tumor in childhood. The incidence of intracranial meningiomas in children is in the range of 1-4% among all childhood brain tumors[3]. Meningiomas are more common in second decade than the first, and are extremely uncommon in infancy. An almost universal finding in childhood meningiomas has been the absence of female predominance seen in adults[3]. The clinical presentation in children differs from adults mostly in infants, where the first sign of tumor may be an increasing head size[4]. Otherwise, the symptoms and signs relate to the site of the tumours. In one series 46% presented with focal neurological deficit, 30% showed signs of raised intracranial pressure and 23% had seizure[3].

In haemophilic patients surgery should be avoided whenever possible, but when necessary, it should be carried out in centre that has the laboratory facilities for monitoring the response to replacement therapy[1]. The preoperative management of patients with haemophilia undergoing surgical procedures and, more specifically, neurosurgical procedures, poses a challenge because of the risk of haemorrhage[4]. Elective surgery in haemophilia patients must be planned several weeks beforehand and requires that adequate notice to be given to the blood transfusion or haemophilia centre. Desired

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factor level in patient's blood in major surgery should be 70-100%[5]. This concentration should be maintained until healing has occurred[6].

We reported our experience with the management of a pediatric patient with haemophilia having refractory epilepsy due to intracranial meningioma.

Case Summary:

Zahid Hossain, a twelve year old boy of class four, from Tangail District, was admitted in the neurosurgery departmentl of Bangabandhu Sheikh Mujib Medical University on 7th January 2008 with the complaints of repeated convulsion of the left side of the body for two and a half years. Initially it involved only the left leg and persisted for one to two minutes. At the beginning it occurred once or twice a month. It was preceded by an aura but was not associated with loss of consciousness or incontinence. Later it gradually involved the whole of the left side of the body with increase in frequency. For this reason he consulted a pediatrician who put him on phenytoin. As his attacks of seizures were not controlled he was switched on to valproic acid, but still the seizures were not controlled. He was then referred to a pediatric neurologist who added carbamazepine and did an EEG which suggested a localized epileptogenic area. Later a CT scan of brain was done which showed a right cerebral space occupying lesion suggesting a meningioma. He was admitted in our department and with the two antiepileptic drugs in optimum dose the boy continued to have seizures. When we detailed his past history, it was revealed that he had persistent bleeding after tooth extraction and circumcision. But there was no positive family history. His coagulation profile showed he had factor VIII deficiency. On physical examination the boy was of average built with other parameters of general examination within normal limit. His neurological examination revealed normal higher psychic function and speech. All cranial nerves were intact, no motor or sensory deficit was found.

Laboratory Data:

TC, DC, ESR, Hb% was within normal limit.

PBF: Anisocytosis with anisochromia.

BT: 3 min 30 sec and CT: 5 min

APTT: Control 28 sec; patient 55 sec

PT: Control 11.8 sec; patient 10.4 sec, INR 0.88

Factor VIII activity: 60%

Factor IX activity: 107.9%

S. Creatinine & Blood urea was within normal limit

X-Ray chest reveal no abnormality

EEG: localized epileptogenic area

CT Scan: hyperdense mass with calcification in right fontal region, after contrast injection, the mass showed intense contrast enhancement.

As the patient had refractory seizure, we decided to resect the tumour. After much effort the patients APTT was kept within normal range on the day of operation by transfusing FFP preoperatively and he was operated on 29.03.08. A right frontal craniotomy and total removal of tumour was done. Postoperative replacement therapy by FFP was continued. The patient developed hemiparesis on the 2nd post operative day and CT scan revealed haematoma in the tumour bed (Fig.-1). We decided not to re-explore and to continue replacement therapy with FFP upto 7th post operative day. His left sided weakness

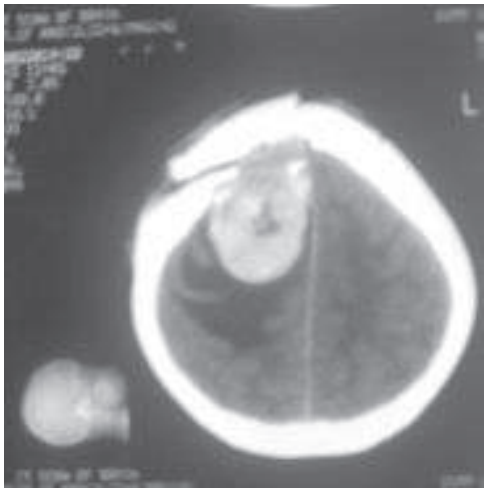

Fig.-1: *Post-operative CT Scan showing haematoma in the tumour bed.*

Fig.-2: *Patient at the time of follow-up after one year.*

improved and was discharged with anticonvulsant. The patient is under our regular follow up for the last one year (Fig.-2). He is now seizure free and has no motor deficit.

Discussion:

Existing studies on surgical management in patients with haemophilia are limited by a lack of data other than case reports of patients undergoing neurosurgical procedures. Even in patients with normal coagulation, surgery on the brain carries the risk of intracranial haemorrhage and death. Patients with haemophilia are at increased risk for intracranial haemorrhage[5]. Emphasis is placed on diagnosing the hemostatic deficiency by the use of four hematological tests: bleeding time, platelet count, partial thromboplastin time, and prothrombin time[8]. Replacement therapy with clotting factors is required for the management of active bleeding episodes and to cover surgical treatment. It consists of intravenous transfusion of plasma derived factor VIII concentrate for haemophilia A and factor IX for haemophilia B. Cryoprecipitate and FFP may also be used[7]. The preoperative work up must also include a coagulation-inhibition screen test. The first dose should be given 1 hour before surgery followed by an assay of the factor level 30 minutes later. Post-operative factor assays are also performed and replacement therapy continued to maintain a level >40% for the first 10 postoperative days[5]. Recently to keep optimum concentration of factors it is suggested to use preoperative bolus dosing followed by continuous infusion during the intra- and postoperative periods[8].

A few successful neurosurgical procedures in haemophiliacs have been published, such as cerebral aneurysm repair, excision of arteriovenous malformations or tumours. However, the decision to undertake a neurosurgical intervention is complex, as excessive bleeding may occur and complicate further the patient's outcome leading to permanent sequelae[9]. Our patient presented with refractory epilepsy due to intracranial space occupying lesion which was radiologicaly consistent with meningioma. Meningiomas in children have intrigued the neurosurgeons for decades[3]. In this case the patient's management was complicated by the presence of haemophilia.

Our hematologist suggested for factor VIII replacement therapy, but the patient was unable to afford the treatment. So fresh frozen plasma (FFP) was used; 3 bags every day for 3 consecutive days to bring the APTT within normal range. It took several cycles of replacement therapies before the APTT could be brought within normal range at the day of operation. Right frontal craniotomy was done with complete removal of tumour. The boy developed weakness of the left side of the body on the 2nd POD. CT Scan was done which showed hemorrhage in the tumour bed. We decided to wait and watch as the patient showed no signs of raised intracranial pressure with motor deficit only. We continued the FFP transfusion till 7th POD. The boy's weakness gradually improved and he was discharged. His histopathology revealed fibroblastic meningioma. He was discharged with the advice to take both valproic acid and carbamazepine. The patient is under our regular follow up. He has recovered from his weakness and had no episodes of seizure after the operation.

Conclusion:

We have described a successful neurosurgical intervention in a haemophilic patient. The success depended on close communication between the haematologist and the neurosurgeon. Thus with adequate replacement therapy and careful monitoring neurosurgical intervention can be considered in a haemophilic patient.

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