VOL. 34 NO. 1 ISSN 1023-4853 January 2018

BANGLADESH JOURNAL OF NEUROSCIENCE

CONTENTS

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Bangladesh Journal of Neuroscience

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- Review articles are subject to the peer review process. They should contain a maximum of 4000 words and 75 references.
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ORIGINAL ARTICLES

Accuracy of Gene-Xpert In Diagnosis of Suspected Tuberculous Meningitis

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Abstract:

Background: *The diagnosis of Extra Pulmonary Tuberculosis, especially tubercular meningitis (TBM) is challenging due to frequent atypical clinical presentation, inadequate clinical sample, and paucibacillary nature of the biological samples, which frequently results in a delay or deprivation of treatment. A semi quantitative, nested, real time PCR Gene-Xpert test is showing promising result in diagnosing pulmonary TB diagnosis, but its role in TBM is yet to be validated.* ***Methods:*** *It was a cross sectional observational study carried out on 40 clinically suspected TBM patients admitted in neuromedicine, medicine and pediatric medicine at CMCH. Clinical, radiological evaluation and conventional tests were done before PCR (Gene-Xpert) using cerebrospinal fluid.* ***Results****: The mean age of the study population was 28.59 (±16.87) years. Seventeen (42.5%) were male and 23 (57.5%) were female with a male to female ratio of 1:1.35. Out of 40 study cases AFB was presesnt in direct microscopy in only 1(2.5%) case, positive growth on culture in 5 (12.5%) cases and positive Gene-Xpert test in 9 (22.5%) cases. Sensitivity, specificity, PPV, NPV and diagnostic accuracy of Gene-Xpert (PCR) was 44.44%, 96.77%, 80%, 85.71%, and 85.0% respectively considering culture as gold standard. Sensitivity of Gene-Xpert in CSF was 22.5% as compared to culture which was only 12.5 % among the study cases.* ***Conclusion:*** *PCR (Gene-Xpert) is highly sensitive and speed in diagnosis of TBM compared to conventional methods.*

Key words: *Tuberculous meningitis, Gene-Xpert, Cerebrospinal fluid, Culture, Diagnostic accuracy.*

Introduction:

Tuberculosis typically affects the lungs and known as pulmonary tuberculosis (PTB) but it can affect almost any organ system including the lymph nodes, central nervous system (CNS), bones/joints, genito-urinary tract, abdomen (intra-abdominal organs, peritoneum), and pericardium[1]. The worldwide incidence of EPTB cases are increasing and significantly contributing to TB-related morbidity and mortality[2]. WHO estimates 10 million TB each year and approximately 5-15% of all of TB cases develops extrapulmonary involvement[2,3]. CNS tuberculosis usually manifests as tuberculous meningitis (TBM) but tubercular encephalitis, intracranial tuberculoma, or a tuberculous brain abscess may occur. In TBM infection spread to the meninges and represents roughly 1% of all TB diseases. It is the most severe form of TB as it

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causes death or severe neurological defects in more than half of those affected, despite the advancements in available antituberculosis treatment[4]. Morbidity and mortality related to TBM is due to the various neurological complications of TBM like in cranial nerve palsy, constriction of internal carotid, obstruction to cerebrospinal fluid (CSF) flowing. Vasculitis that develops due to the inflammatory process is the most serious consequence of TBM[5,6]. Numerous studies have been conducted in search of more rapid, sensitive and specific methods of diagnosis for TBM and these methods include definite microbiological confirmation such as culture, smear, Polymerase chain reaction (PCR) and supportive diagnostic methods such as radiographic assessments, cytology analysis, antibody and antigen detection, and GC-MS[4]. The identification of MTB in CSF by culture is the gold standard and various culture techniques have been evaluated for their performance and each have different advantages and disadvantages. Culture on solid medium such as Lowenstein-Jensen (L-J) enables examination of colony morphology but takes long time for the result which is about 28 - 50 days[7,8]. Results can be obtained faster in commercially available automated systems such as Bactec MGIT 960 (Becton Dickinson, Sparks, MD, USA), radiometric Bactec 460 (Becton dickinson, Heidelberg, Germany), MBBact (OrganonTeknika, Boxtel, Netherlands) and ESP II (Difco Laboratories, Detroit, MI,USA) and they are not suitable to use for routine diagnosis due to their high cost, need for expensive lab set up. Although diagnosis based on culture is the reference standard, results are obtained only after 2-8 weeks of incubation which is too slow to aid in clinical decision making, besides the sensitivity of culture to detect M. tuberculosis in CSF sample is low and range from 40-60% as culture is less sensitive in paucibacilliary conditions. Moreover, it also requires appropriate biological hazard containment facilities and aseptic technique that limits its use[9]. Smear microscopy with traditional Ziehl- Neelsen stain is a rapid and practical method for routine analysis due to its low cost, and high predictive value[10]. The sensitivity of Ziehl-Neelsen stain in detecting acid-fast bacilli (AFB) in CSF is generally low and range from 10-60%[9]. Moreover, large volume (10-15ml) of CSF is required for a more sensitive result which is difficult to obtain in children who have a low total volume of CSF [11]. Nucleic acid amplification technique (NAAT) such as PCR for detection of mycobacterial DNA has been reported to be more rapid, sensitive and specific[3,13]. Studies show the sensitivity of PCR assay for TBM range from 31% to 100% and specificity from 66% to 100%. The paucibacilliary nature and presence of amplification inhibitor in CSF specimen are the main challenges of applying the PCR method to detect M. Tuberculosis[14]. Moreover, the cell wall of M. tuberculosis is made of an impermeable complex structure that makes the lysis of the cell difficult and thus result in poor quality and low yield of nucleic acids when simple and common nucleic acid isolation procedures are used[15]. Physical methods of lysis such as shock treatment (freezing and heating) or Triton X-100 treatment combined with any other DNA extraction procedures are shown to improve the yield of nucleic acids isolated from M. tuberculosis for PCR preparation[16]. Several M. tuberculosis DNA-specific sequences such as IS6110 insertion sequence, protein antigen B, MPB64 and 65kDa have been evaluated by NAA assays[17]. MPB64 gene is regarded the most specific sequence for PCR assay in the detection of M. tuberculosis and had been used as a target sequence in many studies. The sensitivity and specificity of PCR assay targeting MPB64 gene in these studies showed a relatively good result, ranging 75-100% and 100% respectively[18]. Moreover, limited number of gene can be analyzed[19]. The Gene-Xpert MTB/RIF System (Cepheid, Sunnyvale, CA, USA) is a fully automated, single use closed-cartridge-based real-time PCR that performs sample decontamination, sonication, automated nucleic acid amplification, and fluorescence-based quantitative PCR[15]. It can detect MTB and rifampicin susceptibility simultaneously within two hours with high accuracy for the detection of pulmonary TB (sensitivity 89%, specificity 99%) and rifampicin resistance (sensitivity 95%, specificity 98%). Gene-Xpert MTB/RIF had been approved by WHO for M.

tuberculosis detection in sputum while its diagnosis value for the detection of non-respiratory TB is uncertain[20]. A systemic meta-analysis by Denkinger and colleagues (2014) show that the sensitivity of GeneXpert for extra-pulmonary TB varied widely across different sample types in which the detection rate for TBM was only moderate[21]. Studies with extrapulmonary TB samples have been reported promising in smear positive samples compared to smear-negative specimens. It is reported by Nhu and colleagues (2014) that the sensitivity of GeneXpert MTB/RIF for diagnosing TBM was lower than smear and culture (59.3% Vs 78.6% and 66.5%)[22]. Larger studies to assess the usefulness of GeneXpert MTB/RIF for diagnosis of TBM are required. At present, there are few literatures regarding information on TBM diagnosis by PCR and particularly the effectiveness of GeneXpert solely on TBM, therefore the study was undertaken to evaluate the performance of Gene-Xpert assay in diagnosis of TBM.

Materials and methods:

This hospital based cross sectional study having both analytical and descriptive components was conducted in the department of Neurology, Department of medicine, Department of Pediatric medicine of Chattagram Medical College Hospital and Bangladesh Institute of Tropical and Infectious Disease. All the patients admitted in the above mentioned wards of CMCH with clinical diagnosis of TBM. All patients admitted to ward with suspected TBM were assessed for eligibility. Written consent from the patients or attendants was taken after explaining outcome, complications and purpose of the study and right to withdraw from the study at any stage. Patient's history including demographic information, clinical findings, results of laboratory, and neuroimaging testing was recorded in case record form. Sample of CSF was collected from every patient by a standard procedure. CSF specimens were obtained by standard lumbar puncture procedure performed by trained physician. Approximately 5ml of CSF was obtained; 2 ml of sample were used for total and differential cell count, biochemistry and smear for Gram's and acid-fast bacilli (AFB) staining and remaining 3 ml CSF was used for culture and Gene-Xpert test. Routine, gram and AFB stain, fungal and bacterial culture was done in the Department of Microbiology of CMCH. Gene-Xpert test and culture for MTB was done in Bangladesh Institute of Tropical and Infectious Disease (BITID). All the data were checked and edited after collection. Continuous variables were reported as either means ± SD or median (intraquartile range), and categorical variables were reported as percentages. Baseline characteristics were compared by either independent sample Kruskal Wallis test for continuous variables or the χ^2 test for categorical data among different TBM groups. For GeneXpert test, sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated and 95% confidence intervals were estimated. For analytical comparison, mycobacteria culture was considered as gold standard. Statistical significance was defined as $P<0.05$ and confidence interval set at 95% level.

Results and observations:

Total 40 suspected cases of tubercular meningitis were enrolled in the study. As per clinical case definition they were finally classified as follows :

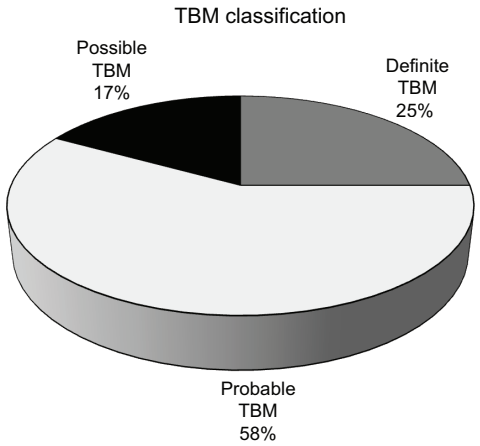

Fig.-1: *Tuberculous meningitis classification of the study subjects.*

Socio-demographic characteristics:

Table I shows the socio-demographic characteristics of the studied patients. Mean age is 28.59±16.87 years with female predominance (male to female ratio=1:1.35). Majority was from

urban area (57.5%), and had educational qualification up to or below primary level (65.8%).

Vaccination status and closed contact with TB patients

Out of 40 suspected TBM cases, 37 (93%) were vaccinated against TB and 12 (30%) had positive history of closed contact with TB patient.

Diagnostic methods by CSF analysis

Collected CSF from the patients was subjected to AFB staining (ZN staining) and microscopy, culture by Lowenstein Jensen media and Gene-Xpert test.

Out of 40 patients AFB was seen in direct microscopy in only 1(2.5%) case, positive growth in culture in 5 (12.5%) cases and positive Gene-Xpert test in 9 (22.5%) cases (Table VIII).

Diagnostic accuracy of Gene-Xpert in comparison to AFB Culture of CSF

Table IV shows the diagnostic reliability of Gene-Xpert test considering the CSF culture test as standard. It reveals that, sensitivity, specificity, PPV, NPV and diagnostic accuracy of Gene-Xpert test is 44.44%, 96.97%, 80%, 85.71% and 85.0% respectively.

Table-I

Socio-demographic characteristics of the patients (n=40)

Variables		
	<20 years	12 (30%)
Age(yrs)	20-30 years	14 (35%)
	>30 years Mean ±SD	14 (35%)28.59 ±16.87
Gender	Male	17(42.5%)
	Female	23 (57.5%)
	Rural	17 (42.5%)
Residence	Urban	23 (57.5%)
	Illiterate	4 (10.5%)
	Primary	21 (55.3%)
Education (n=38)	Secondary	4 (10.5%)
	Higher secondary & above	9 (23.7%)

Table-II

Vaccination status and H/O TB contact of the patients (n=40)

Variables	Total (n=40)	Possible (n=7)	Probable TBM (n=23)	Definite TBM TBM (n=10)	P value
Vaccinated	37 (93%)	7 (100%)	21 (91%)	9 (90%)	0.705
Positive contact history[a]	12 (30%)	1 (14.3%)	7 (30%)	4 (40%)	0.521

Chi-square test was performed to calculate statistical association. P<0.05 was taken as significance.

Table-III

Cerebrospinal Fluid analysis result

Diagnostic tests	Positive result
AFB stain	1 (2.5%)
Culture	5 (12.5%)
Gene-Xpert	9 (22.5%)

Data are presented as number (%).

Table-IV

Comparison of GeneXpert with ABF culture of CSF suspected TBM (n=40)

CSF culture result	GeneXpert result (n)	
	Positive	Negative
Positive (5)	4	1
Negative (35)	5	30
Total (40)	9	31

(Mc Nemar test was done)

Discussion:

CSF from 40 suspected TBM cases were subjected to PCR test detect MTB in order to see its sensitivity and specificity as Gene-Xpert is under evaluation for CSF and other body fluid specimen. The peak incidence in the present study was found in young adults, age group of 20-39 years which is similar to as reported by Sarkar et al., (2013)[24]. In the current study incidence of TBM was higher in female than male. As the study population was small and drawn purposively from a single institute it might not reflect real scenario. However, in contrast to PTB, preponderance for EPTB is reportedly higher among females[25].

In the present study, history of fever is present in all of the cases (100%) which was close to study by 92% in Sarkar et al., (2013). Seizures of generalized tonic and clonic type were noted 15% of our cases while reported 8.3% in Sarkar et al., (2013)[26]. The signs of meningeal irritation was present as neck rigidity or as Kernig's sign in 100% cases while cranial nerve palsies were observed in 43% of the cases, which is consistent with the other study from Bangladesh (42.5%) (Sarkar et al., 2013) but slightly lower than that of Indian study (Khatua et al., 1961) where it was 50%[26, 27.]The commonest was 6th nerve palsy (12/17 cases), then 3rd nerve (3/17 cases) and other two were multiple cranial nerve palsy (2nd & 6th and 6th & 7th). In the present study, the incidence of papilloedema was 40%. Motor impairment in the form of limb weakness was noted in 20% cases, slightly higher incidence was of limb weakness in 23% cases was reported by Marais et al., (2010)[23] and median duration of the prominent symptoms in our study was 30 days (Intraquartile range: 30 to 60 days). Twenty two (60%) of our cases had CT/MRI findings compatible with TBM. The contribution of cerebral imaging to the diagnosis of tuberculous meningitis is well established, although it is not essential to establish a diagnosis of deûnite or probable disease[23]. In our study most prevalent feature was infarction (25%), followed by tuberculoma (20%) and hydrocephalous (10%).

Out of 40 suspected TBM cases, Gene-Xpert was positive in 9 cases while L-J culture detected mycobacteria in 5 cases only. Sensitivity of Gene-Xpert was 22.50% as compared to culture showing a sensitivity of 12.5%. Gene-Xpert could detect additional 4 (10%) cases over L-J culture. Sensitivity of Gene-Xpert in the current study is comparable to other studies who have but lower sensitivity was also reported[27-29]. Paucibacillary nature of TBM, low volume of CSF and small sample size may be the probable reason for low positivity of Gene-Xpert in CSF. Immuno-suppression due to HIV/AIDS or age (e.g., infants, elderly) are key drivers of TBM, and immuno-suppression increases the bacillary burden of MTB organisms. Studies reported higher sensitivity in CSF of TBM in HIV cases[22,30]. Higher yield was recorded in volumes of centrifuged CSF among HIV infected persons with sensitivity of approximately 80% and associated with specificity for microbiologically confirmed TBM. But lower sensitivity of d"50% was recorded with uncentrifuged CSF. This difference in sensitivity associated with centrifugation was not observed in non-HIV cases. The Xpert system dependes upon capture and lysis of whole bacilli, and therefore high volumes (>7 ml) of CSF are crucial to achieving high sensitivity.[31] Bacterial loads are higher in HIV-infected TBM patients, consequently higher detection rate in all the tests for TBM. In our study no HIV-infected patient was included there was small variation from infant and elderly group. Besides only 5 ml of CSF was collected for the laboratory purpose. Rifampicin resistance was not detected among our cases which is in contrast to 3.7% resistance reported in study by Nhu et al., (2014)[22]. The reason for this may be due to inclusion of new cases in the current study. CSF from 12.5% cases were positive by L-J medium culture in our study and while only 2.5% sample was positive by AFB smear examination. The lower positive for AFB smear and culture in the present study is comparable with study by Poonam et al., (2007)[32]. This low yield of AFB smear and culture may be due to the paucibacillary nature of CSF samples; besides, inadequate volume of samples may give low positive result[33]. Negative AFB smear might be due to the low concentration of mycobacteria in those samples i.e. below the detection limit of 10000 organism/ml. Culture

negative might be explained by the absence of viable mycobacteria in the samples[34]. Nhu et al., (2014) found an exceptionally high sensitivity of smear microscopy and explained that this exceptional sensitivity depends upon the proper sample processing, meticulous examination of individual slides for 30 min by a highly skilled and experienced technician[22]. This may be difficult to replicate outside a dedicated research setting due to the work burden in public health laboratories of resource-limited countries like ours[31]. Similar to our finding Sarkar et al., (2013) also observed 100% negative smear microscopy [24].

Hillemann et al., (2011)[35] observed in their study that, in some cases, the GeneXpert assay result was positive but the culture remained negative. Of the seven patients with discrepant results, two patients had pulmonary TB, proven by several cultures of different specimens. Two patient had TB (culture conûrmed) 1year and 2years before and were presumably still or again under treatment at the time of sampling. an indication for the resolution of the discrepancies[35].

TBM is the most severe form of tuberculosis where microbiological confirmation is rare, and treatment is often delayed resulting in increasing mortality and morbidity. The Gene-Xpert MTB/RIF test would be a promising diagnostic tool for early diagnosis of TBM.

Conclusion:

Our study found that Gene-Xpert had higher sensitivity compared to other diagnostic modalities currently available in our setting. High specificity of the assay explains the low false positivity achieved by this diagnostic tool, which can thus be a useful rule-in test for TBM diagnosis.

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Bangladesh Journal of Neuroscience 2018; Vol. 34 (1): 9-16

Association between Serum Thyroid Hormone Levels and Functional Outcome in Acute Ischemic Stroke Patients

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Abstract

Background and Objectives: *Neuroendocrine profile is significantly altered in acute ischemic stroke. Objective of the study was to determine association between serum thyroid hormone levels and functional outcome in acute ischemic stroke patients.* ***Method:*** *It was a cross sectional analytical study which was conducted in the Department of Neurology, BSMMU, Dhaka. Total 60 acute ischemic stroke patients within 14 days of onset of symptoms confirmed by neuroimaging were selected purposively from department of Neurology, BSMMU. Blood sample was collected from the patient on admission, and was analyzed at the Department of Biochemistry, BSMMU for estimation of serum Thyroid hormones (FT3, FT4, TSH) level. Modified Rankin Scale (mRS) score was done after 1 month of stroke. Poor outcome was defined as mRS>2 and good outcome was defined as 0-2.* ***Result:*** *Among Sixty patients 39(65%) had normal FT3 level and rest 21(35%) had low FT3 level.The mean (± SD) serum FT3 Level was 2.77 (±0.99) pmol/L in poor outcome group and 3.67 (±0.65) pmol/L in good outcome group which was statistically significant (p=0.001).A negative correlation co-efficient (r = -0.380) was found between mRS score and serum FT3 concentration,which was also statistically significant (p=0.001).On logistic regression analysis, low serum FT3 concentration remained independent predictor of poor outcome of acute ischemic stroke patients (p=0.001, Odds Ratio = 3.567).* ***Conclusion:*** *In patients with acute ischemic stroke lower serum FT3 level was significantly associated with poor functional outcome.*

Key words: *Acute ischemic stroke, Serum FT3, mRS score.*

Introduction:

Stroke is one of the major global health problems. According to WHO Fact Sheet[1] stroke is the second most common cause of death throughout the world and is the most common cause of severe adult physical disability. However according to GBD 2015 stroke is the number one cause of death in Bangladesh and is also common cause of physical disability. About one-fifth of patients with an acute stroke die within a month of the event and at least half of those who survive are left with physical disability[2]. The reported prevalence of stroke in Bangladesh is 0.3%[3]. The high number of disability-adjusted life-years lost due to stroke (485 per 10,000 people) show that stroke severely impacts Bangladesh's economy[3]. Stroke can be classified into two major categories like ischemic and hemorrhagic. Ischemic strokes are those that are caused by interruption of the blood supply, while hemorrhagic strokes are the ones which result from rupture of a blood vessel. Most embolic strokes characteristically occur suddenly and the deficit reaches its peak almost at once. Thrombotic strokes may have an abrupt onset, but they evolve somewhat more slowly over a period of several minutes or hours and occasionally days; in the latter case, the stroke usually progresses in a saltatory fashion. In hypertensive cerebral hemorrhage, also abrupt in onset, the deficit may be virtually static or steadily progressive over a period of minutes or

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hours, while subarachnoid hemorrhage is almost instantaneous[4,5]. Pituitary thyroid axis is significantly altered in patients with acute stroke[6]. Low triiodothyronine (T3) level has been shown to be associated with increase in short term mortality in intensive care unit patients and increased long term mortality in patients with heart disease[7,8]. This is known as nonthyroidal illness syndrome (NTIS) or sick euthyroid syndrome. Abnormalities of thyroid function in NTIS have been classified as low T3 syndrome, low T3-low T4 syndrome, high T4 syndrome and other abnormalities[7]. The most common pattern is a decrease in T3 level with normal level of thyroxine (T4) and thyroid stimulating hormone (TSH)[9,10]. This is known as low T3 syndrome. In more severe illness T3 and T4 level are reduced while TSH level does not show expected pituitary thyroid axis reactivity[9]. This is known as low T4 syndrome. Serum TSH in NTIS is typically normal or reduced. Some patients are found with a TSH level above normal and elevation of TSH above normal commonly occurs if patients recover[10]. Low T3 syndrome is common in critically ill patients, and it has been well demonstrated that low T3 syndrome was independently associated with greater mortality rate and worse functional outcomes across different populations of patients, including patients after acute cardiac events[11], patients with respiratory failure[12], intensive care unit patients[13], and after surgery for brain tumor[14]. Similar results were also reported in stroke patients. For example, it has been shown that ischemic stroke patients with low T3 syndrome were at increased risk for poor functional outcome at follow-up that was scheduled from 2 to 4 weeks after ischemic stroke[15]. Another study found that 1-year survival was significantly worse in stroke patients with low T3 syndrome[16]. Also, a study from India reported that lower total T3 concentrations were associated with poor neurological presentation and worse clinical outcome 7 days after acute stroke[6]. All the studies mentioned above investigated total T3 concentration. Some studies also reported low FT3 levels are related to poor prognosis in acute ischemic stroke patients[17,18,19]. Whereas an increase in TSH level has been described to be associated with better outcome in stroke patients in some studies[16,17]. So the probable correlation between alteration of thyroid hormone and severity of stroke and its outcome needs further investigation.

Materials and Methods:

It was a cross sectional Analytical study conducted in the Department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. All adult acute ischemic stroke patient of both sex, meeting the inclusion and exclusion criteria were included in the study.

Total 60 (sixty) acute ischemic stroke patients within 14 days of onset of symptoms who admitted in the inpatient ward of Department of Neurology, BSMMU were selected and enrolled purposively for the study. Informed written consent was taken from each patient or from patient's attendant. Detailed history was taken from each patient and through physical examination was performed. Partial demographic profile including age, sex, residence, occupation, marital status, educational level, income status was recorded. Information regarding hypertension, smoking, diabetes, ischemic heart disease, valvular heart disease and other relevant history were recorded through a structured questionnaire. Stroke severity was assessed on the basis of National Institutes of Health Stroke Scale (NIHSS) on admission. Blood sample were collected for serum thyroid hormone (FT3, FT4, TSH) levels measurement within the first 2 weeks of the onset of stroke symptoms in the Department of Biochemistry at BSMMU. Serum thyroid hormone was measured by chemiluminescent microparticle immunoassay (Abbot Architect ci 8200, co-USA). All other relevant investigations (Plasma glucose level, Fasting lipid profile, Serum creatinine, ECG, Echocardiogram) were also done in BSMMU. On day 30 functional outcome was assessed by using the modified Rankin Scale (mRS). Total patients were divided into two groups according to functional outcome as poor outcome and good outcome. Poor outcome was defined as mRS>2 or death and good outcome as mRS 0-2[19]. All the data were checked and edited after collection. Continuous variables were expressed as Mean ± SD. Categorical variable was presented by frequency, percentage and graph. Qualitative data were analyzed by chi-square test. Quantitative data were analyzed by unpaired t-test. Pearson's correlation coefficient test was done to see the correlation between variables. Logistic regression analysis was used to evaluate association of other variables. p value of < 0.05 was considered statistically significant. Statistical

analysis were done using SPSS (Statistical package for social sciences) windows version 22 software programme.

Results:

The mean age (±SD) of the study population was 59.16 (±12.30) years with a range from 30 to 81 years. The mean age of the good outcome group (mRS 0-2) was a bit lower than that of poor outcome group (mRS>2). Regarding sex 56.7% patients were female and 43.3% male. Male and female ratio was 1: 1.3. (Table I). Study population by NIHSS, it was found 27(45%) patients with minor stroke, 31(51.7%) patients with moderate stroke and 2(3.3%) patients with moderate to severe stroke (Table I). Thyroid hormone status in study population, it was found that serum FT3 level was decreased in 21(35%) Patients but FT4 level was decreased in only 2(3.3%) patients and TSH level in 4(6.7%) patients (Table II).

The mean value of serum FT3 level level in poor outcome group were found lower than good functional outcome group which was statistically significant ($p<0.05$) (Table III). Significant association ($p<0.001$) of serum FT3 concentration with mRS after 1 month of stroke (Table V) was found. Significant association ($p<0.005$) was also found of admission NIHSS with mRS after 1 month of stroke. Moderate and moderate to stroke type of stroke are statistically significant with outcome (Table VI).

Correlation between serum FT3 level and outcome after 1 month (based on mRS score). Pearson's correlation coefficient test was done. Here we found negative correlation co-efficient (r_s= -0.380) which was statistically significant (p=0.001) (Fig. 1). Logistic regression analysis was done for prediction of acute ischemic stroke outcome within one month. It revealed that Age, hypertension, family history, NIHSS and serum FT3 level were found independent predictor for acute ischemic stroke outcome within one month.

Table I shows the demographic profile of the study population .The most frequent age group was 51-60 years representing 33.3%. Male and female ratio was 1: 1.3. Most of the patients 29(48.3%) were housewife.

Table-I

Distribution of the study population by demographic variables according to outcome (Based on mRS score) (n=60)

Characteristics	Good outcome (mRS 0-2) n(%)	Poor outcome (mRS>2) n(%)	Total n(%)	P value
Age in years				
30-40	6(18.8)	0(00)	6(10)	0.054^{ns}
41-50	4(12.5)	6(21.4)	10(16.7)	
51-60	12(37.5)	8(28.6)	20(33.3)	
61-70	8(25)	10(35.7)	18(30)	
>70	2(6.2)	4(13.3)	6(10)	
Mean±SD	56.31±12.52	62.42±11.40	59.16±12.30	
Range	30-75	45-81	30-81	
Sex				
Male	12(37.5)	14(50)	26(43.3)	0.330^{ns}
Male female ratio	1:1.3			
Monthly income				
5000-10000	1(3.2)	3(10.3)	4(6.7)	0.405^{ns}
10000-20000	8(25.8)	8(27.6)	16(26.6)	
20000-30000	13(41.9)	6(20.7)	19(31.7)	
30000-40000	5(16.1)	6(20.7)	11(18.3)	
>40000	4(12.9)	6(20.7)	10(16.7)	

Table II

Distribution of the study population by NIHSS on admission (n=60)

NIHSS	Number	Percentage
Normal/near normal (0-1) examination	0	00
Minor stroke (1-4)	27	45.0
Moderate stroke (5-15)	31	51.7
Moderate to Severe Stroke (15-20)	2	3.3
Severe stroke (>20)	0	00

Table II shows distribution of study population by NIHSS. It was found 27(45%) patients with minor stroke, 31(51.7%) patients with moderate stroke and 2(3.3%) patients with moderate to severe stroke.

Table-III

Thyroid hormone status on admission in study population (n=60)

Serum thyroid hormone	Number	Percentage
FT3		
Decreased	21	35.0
Normal	39	65.0
FT4		
Decreased	2	3.3
Normal	58	96.7
TSH		
Decreased	4	6.7
Normal	56	93.3

Table III shows thyroid hormone status in study population. It was found that serum FT3 level was decreased in 21(35%) patients.

Table-IV

Distribution of mean serum thyroid hormones level in study population according to functional outcome group. (n=60)

	Good functional outcome (mRS 0-2)	Poor functional outcome (mRS>2)	P value
FT3pmol/L	3.67±0.65	2.77±0.99	0.001^{s}
FT4pmol/L	13.52±1.11	14.21±2.79	0.200^{ns}
TSHmIU/L	2.91±0.99	2.38±1.01	0.047^{ns}

s=significant, ns=not significant, Unpaired t-test was done to measure the level of significance.

Table IV shows The mean value of serum FT3 level in poor outcome group were found lower than good functional outcome group which was statistically significant($p<0.05$).

Table-V

Association of FT3 level and functional outcome of study population (n=60)

FT3 level	Good functional outcome (mRS 0-2) n (%)	Poor functional outcome (mRS>2) n (%)	P value
Decreased	3(9.4)	18(64.3)	$<0.001^{S}$
Normal	29(90.6)	10(35.7)	
Total	32(100)	28(100)	

S= Significant, Chi-square test was done to measure the level of significance

Table V shows significant association ($p<0.001$) of serum FT3 concentration with mRS after 1 month of stroke.

Table-VI

Association of admission NIHSS level and functional outcome of study population (n=60)

NIHSS	Good functional outcome (mRS 0-2) n (%)	Poor functional outcome (mRS>2) n (%)	P value
Minor stroke	22(68.8)	5(17.9)	0.001^{s}
Moderate stroke	10(31.2)	21(75)	
Moderate to severe stroke	0(00)	2(7.1%)	
Severe	0(00)	0(00)	

S= Significant, Chi-square test was done to measure the level of significance

Table VI showed significant association ($p<0.005$) of admission NIHSS with mRS after 1 month of stroke. Moderate and moderate to stroke type of stroke are statistically significant with outcome.

Table VII

Logistic regression analysis for prediction of acute ischemic stroke outcome within one month (based on mRS score)

Variable	Beta	S.E	P value	OR	95% CI	
					Lower	Upper
Age	1.179	0.592	0.007	3.250	1.018	10.379
Male Sex	0.511	0.526	0.331	0.331	0.600	1.669
Smoking	0.059	0.542	0.914	0.061	0.366	1.070
DM	0.251	0.519	0.629	1.286	0.464	1.559
HTN	1.017	0.669	0.001	8.167	0.093	3.174
Dyslipidemia	0.511	0.568	0.368	0.600	0.197	1.825
Heart disease	2.598	0.710	0.999	0.019	0.111	0.357
Family History	1.275	0.609	0.036	4.572	0.085	0.921
NIHSS (>4)	3.258	0.705	0.001	6.00	6.532	20.498
FT3	2.856	0.723	0.001	3.576	0.014	1.237
FT4	0.426	1.772	0.999	0.112	0.012	0.231
TSH	0.223	1.037	0.830	.800	0.105	2.204

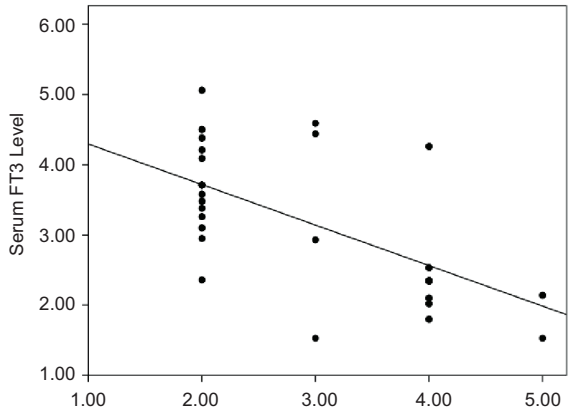

Fig.-1: *Correlation between serum FT3 level and mRS score*

Figure 1 shows correlation between serum FT3 level and outcome after 1 month (based on mRS score). Pearson's correlation coefficient test was done. Here we found negative correlation co-efficient (r_s= -0.380) which was statistically significant (p=0.001).

The table VII shows the result of logistic regression analysis for prediction of acute ischemic stroke outcome within one month. It revealed that Age, hypertension, family history, NIHSS and serum FT3 level were found independent predictor for acute ischemic stroke outcome within one month.

Discussion:

This current study was done with an aim to find out the association of serum thyroid hormone concentration with functional outcome of acute ischemic stroke patients. In this study some relevant risk factors that may affect the outcome and some demographic profile like age, sex, occupation and income status were also evaluated. This was a cross sectional analytical study done on the first ever ischemic stroke patients admitted in the department of neurology, BSMMU from April 2017 to April 2018. A total of 60 patients were assessed in this work. The mean (± SD) age of the study population, was found to be 59.16 ± 12.30 years ranging from 30 to 81years, with a male/female ratio of 1: 1.3. The maximum number (33.3%) of the patients were in the 51-60 years age group. Most of the patients (31.6%) per month family income were in between 20,000 to 30,000 taka followed by 30% patients per month family income were in between 10,000 to 20,000 taka. In a previous study Rahman et al.[20] found that the mean (± SD) age was 64.06± 11.238 years with a male/female ratio of 1.9:1. In another study, Saha et al.[21] found that the mean (± SD) age was 59.97± 12.12 years with a male/female ratio of 1.6:1. Since, both of these studies were conducted on the Bangladeshi population, the results were nearly

similar to one another. However, these demographic profiles are likely to vary when the study population is different. Zhang & Meyer[10] and Delpont et al.[22] found that mean age of 68 ± 12 and 69.4 ± 15.4 years and a male/female ratio of 1.55:1 and 1.56:1 respectively in European population. These results showed that the patients are of older age and the frequency of male patients were higher than females in European population. In contrast, current study population shows the patients were of relatively younger age and frequencies of female slight higher than male. Higher average life expectancy in European people may explain the older age but explanation of differences in sex may be due to acute ischemic stroke patient admitted more in the female ward than male ward of BSMMU during this study period. Considering socioeconomic status most of the patients (31.6%) per month family income were in between 20,000 to 30,000 taka followed by 30% patients per month family income were in between 10,000 to 20,000 taka.

The general objective of this study was to assess the association of serum thyroid hormones level with outcome in acute ischemic stroke patients. Among the thyroid hormones FT3 level was reduced in 21(35%) patients but FT4 and TSH reduced only in two and four patients respectively. The mean (± SD) serum FT3 Level was 2.77 (±0.99) pmol/Lin poor outcome group and 3.67 (±0.65) pmol/L in good outcome group in the present study. Likewise serum FT3 level 2.19 (±0.45) pg/mL in poor outcome group and 2.45 (±0.57) pg/mL in good outcome group (Suda et al., 2016).[17] In another study it was 2.39 (2.12-2.66)pg/mL and 2.54(2.29-2.85)pg/mL respectively (Xu yan et al., 2015)[23]. This may be due to different method of measurement of serum thyroid hormone level. Patients with poor outcome had significant low serum FT3 level than patients with good outcome (2.77 (±0.99) pmol/L versus 3.67 (±0.65) pmol/L). In current study, serum FT3 level on admission was highly significant (p<0.001) with mRS score after 1 month of stroke. This study concluded that decrease serum FT3 level was associated with poor outcome (mRS score>2) of acute ischemic stroke patients. In one study (Delpont et al., 2016)[22] showed that an increase in TSH level was associated with better outcome at discharge. Baek et al (2010) also showed favorable influence of subclinical hypothyroidism on the functional outcome in stroke patients. In the current study we found no such association.

In logistic regression analysis for serum FT3 level variable that the estimated odds ratio (OR) was 3.576, which means the patients with low serum FT3 level have odds to have poor outcome and this was significant at a p-value of 0.001. It was observed that higher concentration on admission is more likely to have favorable outcome in acute ischemic stroke than low serum FT3 level.On one previous study (Xu yan et al., 2016)[23] lower total T3concentrations was found to be independently associated with poor functional outcome (OR= 0.10 ; 95% CI = 0.01-0.84, p =0.035) and in another one (Suda et al., 2016),[17] lower serum FT3 level was found to be an independent predictor of poor outcome (OR= 9.92 ; 95% CI = 4.82-21.33 , p= <0.0001) of ischemic stroke. All of these above mentioned previous studies coincide with the finding of current study. Overall, in all of the studies including the current one, it can be assumed that serum FT3 concentration on admission was associated with functional outcome of acute ischemic stroke.

Conclusion:

In conclusion, this study revealed that lower serum FT3 concentration in acute ischemic stroke is significantly associated with poor functional outcome. So, it might be considered as an important promising prognostic biomarker for assessing the severity, course and prognosis in early stage of the disease and therefore, active management in acute stage would be helpful in decreasing the risk of poor outcome.

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Bangladesh Journal of Neuroscience 2018; Vol. 34 (1): 17-24

Association of Metabolic Syndrome with Migraine: A Case-Control Study

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Abstract:

Background: *Migraine is a disabling primary headache disorder and metabolic syndrome is a major escalating public-health challenge worldwide. They share some common pathophysiology. But till date, their relationship is obscure.* ***Methods:*** *This study was conducted in headache clinic and inpatient-outpatient department of Neurology and Biochemistry laboratory of BSMMU, from June 2017 to February 2019. In these age-sex matched case control study, 30 migraine patient and equal number non migraine volunteer were taken according to inclusion exclusion criteria. Waist circumference (WC), blood pressure (BP), fasting plasma glucose (FPG), serum triglyceride (TG) and high density lipoprotein cholesterol (HDL-C) were measured among all.* ***Results:*** *In this case control study, 24 women and 6 men were taken in both case and control groups, with mean age (±SD) of 32 (±7.77) and 30 (±8.46) years respectively. Metabolic syndrome was significantly higher among migraineurs (36.7% in case and 13.3% in control group respectively, p=0.037). Patient with metabolic syndrome had 3.763 times more chance of having migraine then person without metabolic syndrome [p=0.037, OR=3.763, 95% C.I. (1.038-13.646)].* ***Conclusion:*** *There is an association between metabolic syndrome and migraine.*

Keywords: *Migraine, Metabolic syndrome, oxidative stress etc.*

Introduction:

Migraine is a common disabling primary headache disorder with high socio-economic and personal impacts. In the Global Burden of Disease Survey 2010, it was ranked as the 3rd most prevalent disorder and 7th highest specific cause of disability world-wide[1]. Migraine has two major sub types; migraine without aura (common migraine) and migraine with aura (Classical migraine). Migraine without aura, a clinical syndrome characterized by headache with specific features and associated symptoms.There are recurrent headache attacks, lasting 4-72 hour. Headache typically unilateral, pulsating quality, moderate to severe intensity, headache aggravated by routine physical activity and associated with symptom like nausea and/or photophobia and phonophobia[1]. Migraine with aura is primarily characterized by the transient appearance of focal neurological symptoms which usually precede or sometimes may accompany

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headache. Among different types of aura visual aura is the most common (90%) type[1]. Several theories have been put forward regarding the complex pathophysiology of migraine-the vascular theory, migraine generator theory, the cortical spreading depression theory and the trigeminovascular theory[2]. Activation of the trigeminovascular system plays a central role in the pathophysiology of migraine and linked to the pain of migraine[3]. Activated trigeminovascular system leads to release of inflammatory vasoactive neuropeptides (CGRP, substance-P, NO) from sensory afferents that innervate the major intracranial arteries, results in vasodilation, plasma protein extravasation, inflammation (termed as "neurogenic inûammation")[3]. More and more evidence indicates a primary role for CGRP as a mediator of migraine[2]. Cortical spreading depression (CSD) is hypothesized to cause the aura of migraine, activate trigeminal nerve afferents and alter blood-brain barrier permeability[2]. In migraine, special pattern of inflammatory and oxidative stress markers has been observed in the systemic circulation including increased levels of C-reactive proteins (CRP), interleukins (IL-1, IL-6), TNF-α[4,5]. Increased level of Leptin (activates IL and TNF-α, increase pain sensitivity) [5], Homocysteine (induces neurogenic inflammation, oxidative stress, inhibition of GABA-A receptor in migraine attack)[6] and decreased magnesium level in serum and brain (Mg in the brain triggers release of 5-HT- a vasoconstrictor)[2],have been observed among migraineurs. Migraine is associated with some major vascular diseases including- stroke, subclinical brain matter lesions, coronary artery disease and HTN[7]. The metabolic syndrome is a major escalating public-health problem and clinical challenge worldwide in the wake of urbanization, surplus energy intake, increasing obesity, and sedentary life habits[8]. Metabolic syndrome is present if $\geq$3 of the following five criteria are met: waist circumference >90 cm (men) or >8o cm (women) (adjusted for Asian population), blood pressure Systolic >130 or Diastolic >85 mmHg or on drug treatment for HTN is an alternate indicator, fasting triglyceride (TG) level >150 mg/dl or on drug treatment for elevated TG, fasting high-density lipoprotein (HDL) cholesterol level <40 mg/dl (men) or <50 mg/dl (women) or on drug treatment for reduced HDL-C and fasting blood sugar >100 mg/dl or On drug treatment for elevated glucose[8]. Metabolic syndrome confers a 5-fold increased risk of type 2 DM and 2-4 fold the risk of developing cardiovascular disease and stroke[9].

Though exact pathogenesis of metabolic syndrome is not clear, but abdominal adiposity and insulin resistance thought to be at the core of the pathophysiology of the metabolic syndrome and its individual components[10,11].Free fatty acid (FFA) are released in abundance from an expanded adipose tissue mass, which result in increased hepatic production glucose and triglycerides, leads to the lipid/lipoprotein abnormalities include reductions in HDL-C, reduce insulin sensitivity in muscle & increase pancreatic insulin secretion, resulting in hyperinsulinemia[10,11]. Insulin resistance in the liver, muscle, and adipose tissue is also associated with the abundance of proinflammatory cytokines[10,11]. In obese person elevated calcitonin gene related peptide (CGRP) and Leptin and decreased Adiponectin (an anti-inflammatory substance) have been observed in different studies[12]. Metabolic syndrome is found to be associated with hyperhomocysteinemia[13] and low serum magnesium levels[14].

The relationship between metabolic syndrome and migraine is still obscure and only few studies done regarding this topics[15,] which have found positive[15-20] and negative associations[21]. Among previous studies conducted in BSMMU found migraine is associated with dyslipidemia[22], decreased level of serum Magnesium[23], hyperhomocysteinemia[24] all of them is also associated with metabolic syndrome. Another study in Bangladesh found migraine more severe in patients with comorbidities like DM, HTN and obesity[25].

Materials and methods:

This age-sex matched case control study was conducted in headache clinic and inpatient-outpatient department of Neurology and Biochemistry laboratory of BSMMU. Patients with migraine headache (according to ICHD-3 beta criteria)[1], age more than 18 years, who were willing to participate in this study and who had given informed written consent, were enrolled as case group. Age and sex matched non-migraineur volunteers, age more than 18 years were selected

as control group. Both case and control were enrolled by purposive consecutive sampling technique. Participants had pregnancy or lactating, who were smoker, alcoholic, on active pain (during examination or sample collection), with acute illness (e.g. fever, acute myocardial infarction, acute stroke). had following conditions or diseases: Diabetes mellitus, hypothyroidism, Cushing's syndrome, acromegaly, polycystic ovarian syndrome, chronic kidney disease, nephrotic syndrome, chronic liver disease, who took following drugs: Glucocorticoid, Oral contraceptives, Amitriptyline, Valproic acid, Pizotifen, Beta blocker, Thiazide diuretics, Mirtazapine, Quetiapine, Olanzapine, Retinoids were excluded from this study. Secondary causes of metabolic syndrome along with its individual components were excluded among person whom was suffering from metabolic syndrome. Anthropometric measurements including height, weight, waist circumference (WC) were taken with participants following the standard protocol (participants wearing light clothes and without shoes). Body mass index (BMI) was calculated as the weight (kg) divided by square of the height (m^2). To measure waist circumference (WC), top of right iliac crest were located (WC-IC method). A measuring tape ((standard metered flexible measuring tape) was placed in a horizontal plane around abdomen (tape was snug but non compressive. Measurement (cm) was made at the end of a normal expiration. Blood pressure were measured in the both arms by auscultatory method using standard metered Mercury Sphygmomanometer (Model: ALPK-2), following the AHA, (2005)[26] guideline of blood pressure measurement. Participants were fasted at least 12 hour overnight before blood sample collection.Withall aseptic precaution measures 10 ml of venous blood were collected from each of the participants (using sterile 10 cc disposable plastic syringes). 2 ml of blood were collected in a gray cap test tube (containing EDTA) for measuring fasting plasma glucose and 5ml ofblood were collected in a red cap test tube for measuring fasting lipid profile. Coulter auto-analyzer machine (Model-AU680, USA) was used along with proper reagent to measure fasting plasma glucose and serum lipid profile.Metabolic syndrome was diagnosed according AHA/NHLBI, 2005 criteria[8].

Statistical analysis:

Demographic, anthropometric, clinical and laboratory characteristics (Data) were expressed as mean ± SD (standard deviation) for continuous variables or as percentages for categorical variables. Data were compared by using Student's t-test for continuous variables. For categorical variables, differences were assessed by the Chi-square test. To assess the relative significance of etiological variable, binary logistic regression was used. Results for the binary logistic regression were presented as odds ratios (OR) with a 95% confidence interval (CI). Data were analyzed by using statistics software SPSS v-25. In all cases, P values <0.05 were considered as statistically significant.

Results:

A total number of 60 participants were recruited for this study of which 30 migraineurs were in case group and the 30 respondents were in control group after fulfilling the inclusion and exclusion criteria.

Table-I

Distribution of the Study Groups by Age

Age Group (years)	Groups		P value
	Case	Control	
18 to 25	9 (30%)	11 (36.7%)	0.583 ð ns
26 to 30	7 (23.3%)	7 (23.3%)	1.000 ð ns
31 to 35	6 (20%)	4 (13.3%)	0.488 ð ns
36 to 40	5 (16.7%)	4 (13.3%)	0.717 ð ns
Above 40	3 (10%)	4 (13.3%)	0.687 ð ns
Total	30 (100%)	30 (100%)	0.919 ð ns
Mean ±SD (Years)	32 ± 7.77	30 ± 8.46	0.962 ð ð ns

*p- value was derived from Chi-Squire test, **p- value was derived from unpaired t-test, p-value < 0.05 was considered as significant, ns= not significant, s= significant

Table I shows that, the mean age (±SD) was 32 (±7.77) years in case group. The mean age (±SD) was 30 (±8.46) years in control group. Most of the study patients'ages were 18 to 25 years in case group (30%) and 18 to 25 years in control group (36.7%).

Table-II

Distribution of the Study Groups by Gender

Gender	Groups		p-value
	Case	Control	
Male	6 (20%)	6 (20%)	1.000 ns
Female	24 (80%)	24 (80%)	
Total	30 (100%)	30 (100%)	

Chi-square test was done as a test of significance and p-value < 0.05 was considered as significant, ns= not significant.

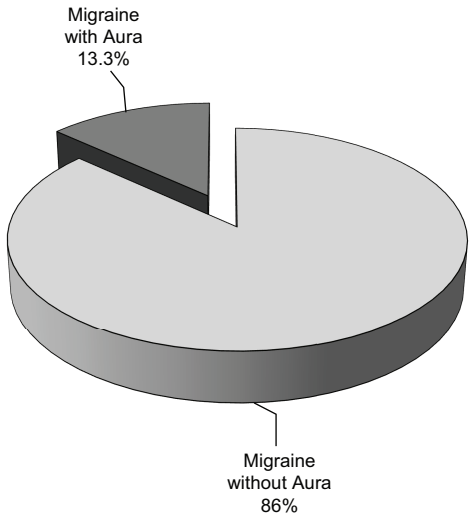

Fig.-1: *Pie Chart Showing Distribution of Migraineurs According to Presence of Aura*

Table-III

Distribution of the Study Groups by Metabolic Syndrome

Metabolic syndrome	Groups		Total	p-value
	Case	Control		
Yes	11 (36.7%)	4 (13.3%)	15 (25%)	0.037 s
No	19 (63.3%)	26 (86.7%)	45 (75%)	
Total	30(100%)	30(100%)	60(100%)	

Chi-square test was done as a test of significance and p-value < 0.05 was considered as significant, s = significant.

Table-IV

Distribution of the Study Groups by Different Variables

Variables	Groups		p-value
	Case (n=30) Mean ± SD	Control (n=30) Mean ± SD	
Height (cm)	154.81±6.39	155.54±7.12	0.676 ns
Weight (kg)	53.72±7.29	53.36±8.22	0.858 ns
BMI [Wt.(kg)/Height (m2)]	22.4±2.57	21.79±2.03	0.315 ns
Waist Circumference (WC) (cm)	86.98±6.55	81.77±4.51	0.001 s
Systolic blood Pressure (SBP)	123.00±11.19	114.17±13.14	0.007 s
Diastolic blood pressure (DBP)	76.50±6.84	73.17±6.23	0.053 ns
Fasting blood glucose (mmol/L)	5.44±0.66	5.20±0.52	0.117 ns
Total cholesterol (TC) (mg/dL)	199.7±40.08	194.53±38.83	0.614 ns
HDL Cholesterol (HDL-C)(mg/dL)	39.47±10.08	45.67±12.68	0.040 s
LDL Cholesterol (LDL-C) (mg/dL)	126.28±35.5	123.3±31.38	0.732 ns
Triglyceride (TG) (mg/dL)	170.13±85.1	126.8±60.87	0.027 s

Unpaired t test was done as a test of significance and p-value < 0.05 was considered as significant, ns= not significant, s= significant.

Table-V

Risk Assessment of Metabolic Syndrome as a Risk Factor of Migraine with Binary Logistic Regression Analysis

Variable	Groups		p-value	OR (95% CI)	
	Case	Control			
Patient with metabolic syndrome	11 (36.7%)	4 (13.3%)	0.037	3.763	(1.038-13.646)

CI=Confidence Interval; Odds Ratio=OR

Table II shows that male and female were equally distributed between case and control groups. Out of 30 participants, male were 6 (20%) and female 24 (80%) in each group.

Table III shows that, 36.7% patient in case group and 13.3% person in control group were suffering from metabolic syndrome. However 63.3% patient case group and 86.7% person in control group had no metabolic syndrome. P value=0.037, which was statistically significant.

Table IV shows that, waist circumference (WC) (p=0.001s), systolic blood pressure (SBP) (p=0.007), triglyceride (TG) level (p=0.0.027) were significantly higher among migraineurs (case group), while high density lipoprotein cholesterol (HDL-C) levels were significantly lower among were significantly (p=0.040). However, there were no statistically significant difference in height (p=0.676), weight (p=0.858), body mass index (BMI) (p=0.315), diastolic blood pressure (DBP) (p=0.053), total cholesterol (TC) (p=0.614), low density lipoprotein cholesterol (LDL-C) (p=0.732), fasting blood glucose (FBS) (p= 0.117) among case and control group.

Table V showed that, Patient with metabolic syndrome had 3.763 times more chance of having migraine then person without metabolic syndrome [p=0.037, OR=3.763, 95% C.I. (1.038-13.646)].

Discussion:

Metabolic syndrome and migraine both are common risk factor of ischemic stroke and cardiovascular disease. They share some common pathophysiology e. g. obesity, dyslipidemia, Insulin resistance, raised Interleukins (IL-1, IL-6), CRP, Leptin, Homocysteine, CGRP and decreased Adiponectin and serum magnesium. But there relationship is obscure[15].This age-sex matched case control study has found that, 36.7% patient in case group (migraineurs) and 13.3% person in control group (non-migraineurs) have been suffering from metabolic syndrome. This result is statistically significant (p=0.037). So migraine headache is associated with metabolic syndrome. Celikbilek et al., (2015)[15] in a study, conducted in Yozgat region (Central Anatolia), have found that, metabolic syndrome associated with migraine (p=0.001). In their study, 33% migraine patients have been suffering from metabolic syndrome. A recent study in Southeast Asia (Bhoi, et al., 2012)[16], has found that, 31.9% migraineurs (n=135) have metabolic syndrome. In both of these studies, number of migraineurs with metabolic syndrome is almost similar to this study. However, Rahim et al., (2007)[29] have found that, prevalence of metabolic syndrome among Bangladeshi population is 13.5% (a study involving 3981 subjects aged >20). This prevalence of metabolic syndrome is almost similar to the control group of this study. So it indicates that, participants of control are approximately representing general population of Bangladesh.

Anthropological measures among the population of this study- height (cm) is 154.81±6.39 and 155.54±7.12 (Mean ± SD) (p=0.676) in case and control group respectively. Weight is 53.72±7.29, 53.36±8.22 (Mean ± SD) (p=0.858) in case and control group respectively. BMI [Wt. (kg)/Height (m^2)] was 22.4±2.57 and 21.79±2.03 (Mean ± SD) (p=0.315) in case and control group respectively. None of which is statistically significant. But waist circumference (cm) 86.98±6.55 and 81.77±4.51 (p=0.001) in case and control group respectively, is significantly higher among migraineurs. Both Salmasi et al., (2012)[21] and Celikbilek et al.,

(2015)[15] have found that, migraineurs have significantly higher BMI and weight circumference then non- migraineurs. Measures commonly have been used for assessing obesity are BMI and waist circumference (WC). Unfortunately, BMI is not considered to be a good estimate of obesity in Asian Indians as they have a characteristic obesity phenotype, with relatively lower BMI but with central obesity[27]. It has been suggested that, fat distributed in the abdominal region, particularly visceral fat is more metabolically important than other fat depots[27]. Bhoi, et al., (2012)[16], in a study conducted in Southeast Asia, has found that, 31.9% migraineurs have metabolic syndrome but only 13 are obese. This indicates different pattern of obesity of people in this region. Increased waist circumference, a marker of central (visceral) obesity, is also a core component of metabolic syndrome. It is relevant to migraine pathophysiologylogy in various mechanisms like- increased interleukins (IL-1, IL-6), TNF-α, CRP, calcitonin gene-related peptide (CGRP), Leptin., homocysteine and decreased adipocetin and low serum magnesium Streel et al., (2016)[18] and Guldiken et al., (2009)[16] also have been found that, migraine is associated with increased abdominal obesity.

Among other components of metabolic syndrome, systolic blood Pressure (SBP) is significantly higher among migraine population than control group (Mean ± SD) (123.00±11.19 and 114.17±13.14 respectively. p=0.007) but there is no significant difference in diastolic blood pressure (DBP) in between migraine and non-migrainure (76.50±6.84 and 73.17±6.23 respectively, p=0.053). Celikbilek et al., (2015)[15] and Salmasi et al., (2012)[21] have found that, migraineurs have significantly increased systolic diastolic blood pressure, then non-migrainure. Now, both mean systolic and diastolic blood pressure among control group is within optimal level (< 120/80mmof Hg) (EHS/ECC, 2018), but systolic blood Pressure (SBP) among migraineurs not optimal (<130/85 mm of Hg) (EHS/ECC, 2018). This might be an indication of endothelial dysfunction and sympathetic over activity- pathology relevant to these disease process.

Among biochemical components of metabolic Syndrome, Triglyceride (mg/dL) [170.13±85.1 and 126.8±60.87 (Mean ± SD) in case and control group respectively, p=0.027] is significantly higher among migraineurs and HDL cholesterol (mg/dL) is significantly lower among migraineurs [39.47±10.08 and 45.67±12.68 (Mean ± SD) in case and control group respectively, p=0.040]. Among other component of lipid profile total cholesterol (TC) [199.7±40.08 and 194.53±38.83 (Mean ± SD) in case and control group respectively, p=0.614] and LDL Cholesterol (mg/dL) [126.28±35.5 and 123.3±31.38 (Mean ± SD) in case and control group respectively, p=0.732] have no significant difference in between case and control group. However, both Salmasi et al., (2012)[21] and Streel et al, (2016)[18], have found that, HDL-C is significantly lower among migraineurs. Celikbilek et al., (2015)[15] have found that, migraineurs have significantly higher triglyceride level in comparison to control group. High triglyceride and low HDL is indistinguishably related to metabolic syndrome and several previous studies have established that, migraine is associated with dyslipidemia. A study previously done in BSMMU (Saleheen et al., 2016)[22] has found that, migraine is associated with dyslipidemia. That study has found, triglyceride is significantly higher among migraineurs [173.67±61.39 and 128.68±46.31 (Mean ± SD) in case and control group respectively, p=0.000]. This result is approximate to the result of this study. This pattern of dyslipidemia (high triglyceride and low HDL) and elevated blood pressure is relevant with cardiovascular and cerebrovascular adverse events.

This study has not found any significant difference of fasting blood glucose (mmol/L) level between case and control group [5.44±0.66 and 5.20±0.52 (Mean ± SD) in case and control group respectively, p=0.117]. Insulin resistance (IR) (a prior stage, in which a person may go through years before developing pre-diabetes followed by type 2 DM) is related to metabolic syndrome and migraine. Fava et al., (2013)[28] have found that, migraine is associated with insulin resistance.So direct

measuring of IR could have given us better idea. This is included in WHO diagnostic criteria of metabolic syndrome (1998). However, in this study, AHA/NHLB, (2005) criteria is used, for which measuring of insulin resistance is not required.

Conclusion:

The study suggests that, the metabolic syndrome is associated with migraine. Though body mass index is higher among migraineurs then non-migraine but it is not statistically significant. But waist circumference (a core component of metabolic syndrome) is significantly higher among migraineurs. Among other different components of metabolic syndrome systolic blood pressure, triglycerides are significantly higher and HDL-C significantly lower among migraineurs in contrast to non-migraineur.

Recommendation:

Though the study was conducted on small sample size, it may be recommended that, metabolic syndrome along with its components should be searched in migraineur, as some commonly prescribed anti-migraine drugs are associated with weight gain, dyslipidemia and insulin resistance.

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Bangladesh Journal of Neuroscience 2018; Vol. 34 (1): 25-31

D-Dimer in Ischaemic Stroke Subtypes

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Abstract:

Background: *Stroke is the third most common cause of death in the developed world after cancer and ischaemic heart disease, and is the most common cause of severe physical disability. Although, there are many patients in Bangladesh suffering from these disorders, systematic research on them, especially serum biological markers of ischaemic stroke are yet to be evaluated. So the objectives of the present study are to see the serum d-dimer among acute ischaemic stroke patient.* ***Methods:*** *This is a hospital based cross sectional study conducted in neurology department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Total 162 cases of acute ischaemic stroke irrespective of their gender were included who were admitted in BSMMU during the period from October, 2012 to October, 2013. Blood sample was taken for d-dimer measurement from each patient and d-dimer was estimated in department of haematology, BSMMU.* ***Results:*** *Among 162 patients with acute ischaemic stroke, it showed that d-dimer level mean was 1.0862 mg/L ± SD 0.9844 with maximum 4.4 and minimum 0.01. D-dimer was highly raised (n=75, 46%; mean 1.6519 ± SD 1.1396; min 0.11 and max 4.4) in early days of 1st week with a descending manner and almost reached normal level (n=87, 54%; mean 0.5986 ± SD 0.4210; min 0.01 and max 2.25) in later half of 2nd week.* ***Conclusion****: The study showed that raised d-dimer (DD) was significantly associated total anterior circulation infarction (TACI) & partial anterior circulation infarction PACI and raised DD was significant differentiating point TACI or PACI from lacunar infarction (LACI) & posterior circulation infarction (POCI) and raised D-Dimer might not differentiate between TACI & PACI.*

Key word: *Stroke, D-dimer, Ischemia etc.*

Introduction:

Acute stroke is characterized by the rapid appearance (usually over minutes) of a non-convulsive, non-traumatic focal deficit of brain function, most commonly a hemiplegia with or without signs of focal higher cerebral dysfunction (such as aphasia), hemi sensory loss and visual field defect or brain-stem deficit. Confusion, memory or balance disturbance are more often due to causes other than stroke. The neurovascular syndromes enable the physician to localize the lesion so precisely that even the affected arterial branch can be specified[2]. It is the abruptness with which the neurologic deficit develops, usually a matter of seconds that stamps the disorder as vascular. Most embolic strokes characteristically occur suddenly, and the deficit reaches its peak almost at once. Thrombotic strokes may have an abrupt onset, but they evolve somewhat more slowly over a period of several minutes or hours and occasionally days; in the latter case, the stroke usually progresses in a saltatory fashion, i.e., in a series of steps rather than smoothly. In hypertensive cerebral hemorrhage, also abrupt in onset, the deficit may be virtually static or steadily progressive over a period of minutes or hours, while subarachnoid haemorrhage is almost instantaneous[3]. Another important aspect of the temporal profile is the arrest and then some regression of the neurologic deficit in almost all except the fatal strokes.

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At one extreme of rapid regression is a focal syndrome that reverses itself entirely and dramatically over a period of minutes or up to an hour; this defines the "transient ischaemic attack" (TIA). Often, an extensive deficit from embolism partially reverses itself within a few hours or days. There are, however, many exceptions, such as the additive effects of multiple vascular occlusions and the progression of a focal deficit that is caused by secondary brain edema surrounding large infarctions and cerebral hemorrhages[2,3].

All acute occlusions occur because of the occlusion of an artery either by local atherosclerotic/ atherothrombotic or by a thrombus stemming from a proximal artery or the heart. When coagulation occurs in an artery or vein, D-dimer levels increase. D-dimer is a reaction product of intravascular thrombus formation, and thrombolysis can be a clue for hypercoagulation in the patient. For patients considered as having ischaemic stroke, the threshold value of D-dimer is an important diagnostic issue[4].

Methods:

This was a hospital based, cross sectional study carried out on the patientswith the diagnosis of first attack of ischaemic stroke within 2 weeks of onset in indoor and outdoor of Neurology department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. The period of study spans from October, 2012 to October, 2013. Age 18 or more, diagnosed patient of ischemic stroke (IS) within first 2 weeks of presentation and diagnosed by combined Oxfordshire Community Stroke Project classification (OCSP) criteria and confirmed by Neuroimaging, patient or patient's attendance willing to participate were included in the study and haemorrhagic stroke, venous stroke, recent or prior history of disseminated intravascular coagulation (DIC), venous thromboembolism (VTE), Pulmonary embolism (PE), cardiac thrombus, sickle cell crisis, major surgery and trauma, Systemic infection/Septicaemia, snake bites, Myocardial infarction in last 3 months and during study period, SGPT > 88 IU/L, serum creatinine > 1.5 mg/dl, recent bleeding diathesis or disorder (GI bleeding or haematuria), pregnancy & or its complication, treated with or on anticoagulant or fibrinolytic or by antithrombotic, recent or prior IM injection or IV cannula within 48 hours and recent Blood transfusion within 1 month were excluded. With the use of a sample size formulae 162 patients were taken as proportion of occurring Ischaemic Stroke among all Strokes = 88%. Between October 2012 to October 2013 in Neurology department, 162 patients of age 18 or more than 18 with first ever IS presented within first 2 wks of symptoms at any age, was included in this study after taking informed written consent. Detailed history and clinical examination was carried for each patient in presence of a consultant neurologist.

The medical records and demographic, clinical, laboratory and radiological records of each patient was examined.All relevant baseline investigations (e.g.- complete blood count, urine R/M/E etc.) were performed. Eachpatientwas diagnosed as IS subtype as total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), lacunar infarcts (LACI), and posterior circulation infarcts (POCI) by Oxfordshire Community Stroke Project classification (OCSP) criteria and was confirmed by neuroimaging (brain CT & or MRI) with excluding hemorrhagic stroke or other intracerebral diseases. Blood sample was taken for d-dimer measurement from each patient within the first 2 weeks of presentation of IS symptoms and before the anticoagulant or t-PA treatment was started and plasma sample was stored at "32°C till estimation in department of haematology, BSMMU.All the data was checked and edited after collection. It was expressed as Mean ± SD. Qualitative data was analyzed by chi-square test and ANOVAand quantitative data was analyzed by t-test and Post Hoc analysis was done by Fisher's least significant difference (LSD) test. p value of < 0.05 was considered statistically significant. Statistical analysis was done using SPSS (Statistical package for social sciences) win version 12 software programme.

Results:

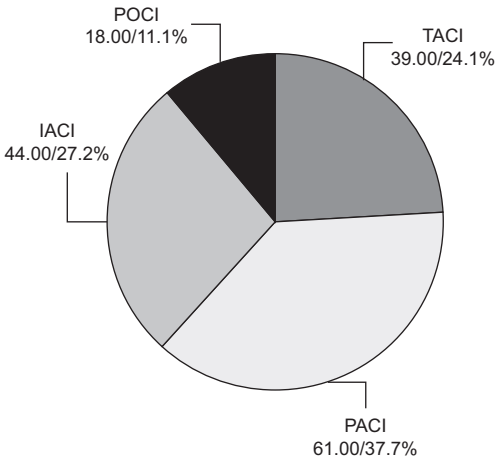

Fig.-1: *Distribution of acute ischaemic stroke patients according to OCSP Ischaemic stroke subtypes (n=162).*

It shows total anterior circulation infarction (TACI) was 39 (24.1%), partial anterior circulation infarction (PACI) was 61 (37.7%), lacunar infarction (LACI) was 44 (27.2%) and posterior circulation infarction (POCI) was 18 (11.1%).

Table-I

Distribution of serum d dimer of acute ischaemic stroke patients (n=162).

D-dimer	N	Min	Max	Mean	Std. deviation (SD)
	162	.01	4.40	1.0862	.9844

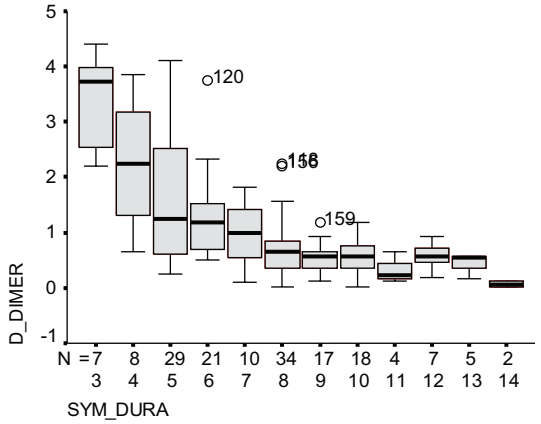

Fig.-2: *Distribution of serum d dimer in each in admission day of acute ischemic stroke patients (n=162)*

Table-I shows serum d-dimer level mean was 1.0862 mg/L ± SD 0.9844 with maximum 4.4 and minimum 0.01.

Figure-2 shows serum d-dimer level value maximum 4.4 and minimum 0.01 with high 1st week level and almost reach normal level at latter part of 2nd weeks with a descending manner.

Table-II

Distribution of serum d-dimer on weekly basis among acute ischemic stroke patients (n=162).

Symptom Duration	Mean	N	SD	Min	Max
First week	1.6519	75	1.1396	.11	4.40
Secondweek	.5986	87	.4210	.01	2.25
Total	1.0862	162	.9844	.01	4.40

Table-II shows serum d-dimer was highly raised (n=75, 46%; mean 1.6519 ± SD 1.1396; min 0.11 and max 4.4) in early days of 1st week with a descending manner and almost reached normal level (n=87, 54%; mean 0.5986 ± SD 0.4210; min 0.01 and max 2.25) in later half of 2nd week.

Table-III

Distribution of serum d dimer of acute ischemic stroke patients according to OCSP Subtypes (n=162).

OCSP Class	Mean	N	SD	Min	Max
TACI	2.1687	39	1.2319	.35	4.40
PACI	1.0995	61	.5781	.35	2.54
LACI	.3659	44	.1996	.01	.70
POCI	.4567	18	.2329	.11	.75
Total	1.0862	162	.9844	.01	4.40

Table-III shows among the 39 patients with TACI, it shows serum d-dimer level mean was 2.1687 mg/L ± SD 1.2319 with maximum 4.4 and minimum 0.35. Among the 61 patients with PACI, it shows serum d-dimer level mean was 1.0995 mg/L ± SD 0.5781 with maximum 2.54 and minimum 0.35. Among the 44 patients with LACI, it shows serum d-dimer level mean was 0.3659 mg/L ± SD 0.1996 with maximum 0.70and minimum 0.01 and it also shows among the 18 patients with POCI, it shows

serum d-dimer level mean was 0.4567 mg/L ± SD 0.2329 with maximum 0.75 and minimum 0.11.

Table-IV

Distribution of serum d dimer on weekly basis in TACI (n=39)

Symptom Duration	Mean	N	SD	Min	Max
First Week	2.8056	25	1.0162	1.18	4.40
Second Week	1.0314	14	.5970	.35	2.25
Total	2.1687	39	1.2319	.35	4.40

Table-IV shows serum d-dimer was highly raised (n=25, 64%; mean 2.8056 ± SD 1.0162; min 1.18 and max 4.4) in 1st week and it also remained above normal level (n=14, 36%; mean 1.0314 ± SD 0.5970; min 0.35 and max 2.25) in of 2nd weeks.

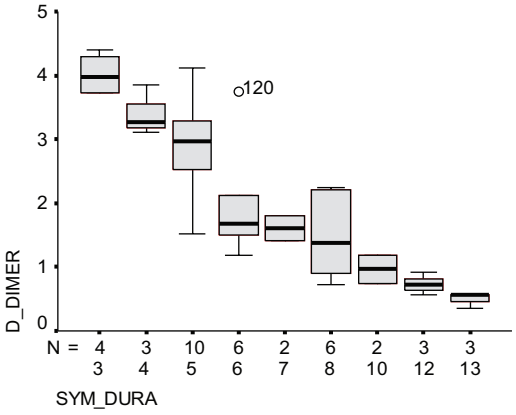

Fig.-3: *Distribution of serum d-dimer in each in admission day of TACI (n=39)*

Figure-3 shows serum d-dimer was highly raised (mean 2.8056; min 1.18 and max 4.4) in early days of 1st week with a descending manner and it also remained above normal level (mean 1.0314; min 0.35 and max 2.25) in whole part of 2nd week with a descending manner.

Table-V

Distribution of serum d dimer on weekly basis in PACI (n=61)

Symptom Duration	Mean	N	SD	Min	Max
First Week	1.6175	24	.5648	.85	2.54
Second Week	.7635	37	.2414	.35	1.55
Total	1.0995	61	.5781	.35	2.54

Table-V shows serum d-dimer was moderately raised (n=24, 39%; mean 1.6175 ± SD 0.5648; min 0.85 and max 2.54) 1st week and it also remained above normal level (n=37, 61%; mean 0.7635± SD 0.2414; min 0.35 and max 1.55) in 2nd week.

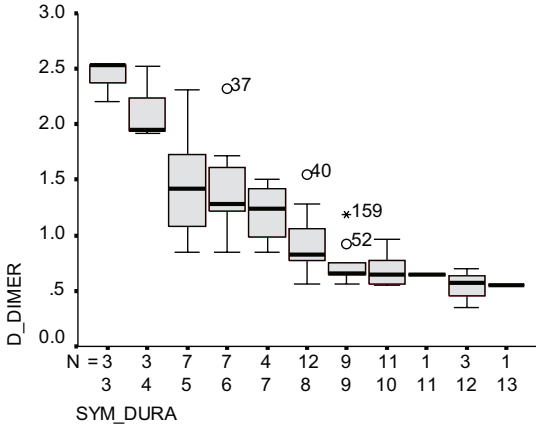

Fig.-4: *Distribution of serum d-dimer in each in admission day of PACI (n=61)*

Figure-4 shows serum d-dimer was moderately raised (mean 1.6175; min 0.85 and max 2.54) in early days of 1st week with a descending manner and it also remained above normal level (mean 0.7635; min 0.35 and max 1.55) in initial half and almost reaches normal in later half of 2nd week.

Table-VI

Distribution of serum d dimer on weekly basis in LACI (n=44)

Symptom Duration	Mean	N	SD	Min	Max
First Week	.5929	14	4.615E-02	.55	.70
Second Week	.2600	30	.1471	.01	.56
Total	.3659	44	.1996	.01	.70

Table-VI shows serum d-dimer was almost normal (n=14, 32%; mean 0.5929; min 0.55 and max 0.70) in 1st week and it also remained within normal level (n=30, 68%; mean 0.26 ± SD 0.1471; min 0.01and max 0.56) in 2nd week.

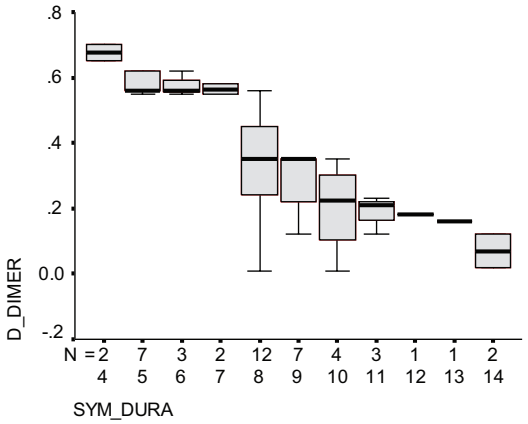

Fig.-5: *Distribution of serum d dimer in each in admission day of LACI (n=44).*

Figure-5 shows serum d-dimer was almost normal with early little rise (mean 0.5929; min 0.55 and max 0.70) in 1st week with a descending manner and it also remained within normal level (mean 0.26; min 0.01and max 0.56) throughout the 2nd week.

Table-VII

Distribution of serum d dimer on weekly basis in POCI (n=18)

Symptom Duration	Mean	N	SD	Min	Max
First Week	.5929	14	4.615E-02	.55	.70
Second Week	.2600	30	.1471	.01	.56
Total	.3659	44	.1996	.01	.70

Table-VII shows serum d-dimer was almost normal (n=12, 67%; mean 0.5525 ± SD 0.2004; min 0.11 and max 0.75) in 1st week and it also remained within normal level (n=6, 33%; mean 0.2650± SD 0.1732; min 0.12 and max 0.59) in the 2nd week.

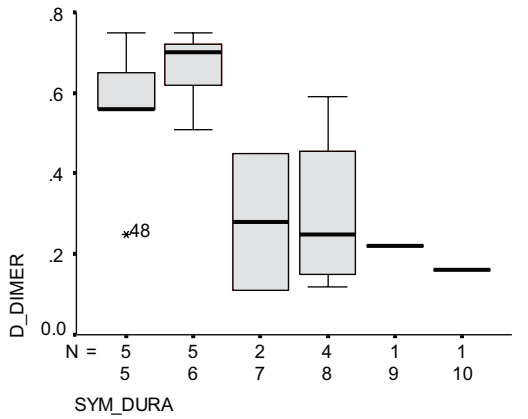

Fig.-6: *Distribution of serum d dimer in each in admission day of POCI (n=18).*

Figure-6 shows serum d-dimer was almost normal with early little raise (mean 0.5525; min 0.11 and max 0.75) in 1st week with a descending manner and it also remained within normal level (mean 0.2650; min 0.12 and max 0.59) throughout the 2nd week.

Discussion:

In Bangladesh prevalence of stroke above age of 40 is 370 per 1,00,000. About 350 patients admitted with stroke in BSMMU in Neurology unit per year[5]. In this study, among the 162 patients with acute ischaemic stroke, total anterior circulation infarction (TACI) was found 39 (24.1%), partial anterior circulation infarction (PACI) were reveals 61 (37.7%), lacunar infarction (LACI) were found 44 (27.2%) and posterior circulation infarction (POCI) were found 18 (11.1%). According to Dewan et al., out of 151 patients with ischaemic stroke admitted in Dhaka medical college from September 2010 to august 2011, reported as non-lacunar stroke (79.47%) was predominant than lacunar stroke (20.52%)[6]. In a study at the National Hospital Abuja, Nigeria between January 2010 and June 2012 where all patients presenting with acute stroke were prospectively recruited and among 163 patients with ischemic stroke, stroke subtypes composed of TACI (19.9%), PACI (43.5%), POCI (17.4%) and LACI (19.3%)[7]. In the study at Sun Yat-Sen University, Zhuhai and at Zhuhai People's Hospital, China from July 2002 to July 2009 where young patients (aged between 18 and 45 years) with first-ever acute stroke who were hospitalized, were included and findings of cases of IS using the OCSP criteria were 15 (6.7%) total anterior circulation infarcts (TACI), 117 (52.0%) partial anterior circulation infarcts (PACI), 61 (27.1%) lacunar infarcts (LACI), and 32 (14.2%) posterior circulation infarcts (POCI) [8].

In this study, among the 162 patients with acute ischaemic stroke, it shows serum d-dimer level mean was 1.0862 mg/L ± SD 0.9844 with maximum 4.4 and minimum 0.01 and normal serum d-dimer level is < 0.55 mg/L. Serum d-dimer was highly

raised (n=75, 46%; mean 1.6519 ± SD 1.1396; min 0.11 and max 4.4) in early days of 1st week with a descending manner and almost reached normal level (n=87, 54%; mean 0.5986 ± SD 0.4210; min 0.01 and max 2.25) in later half of 2nd week. In this study, among the 39 patients with TACI, it shows serum d-dimer level mean was 2.1687 mg/L ± SD 1.2319 with maximum 4.4 and minimum 0.35. Serum d-dimer was highly raised (n=25, 64%; mean 2.8056 ± SD 1.0162; min 1.18 and max 4.4) in early days of 1st week with a descending manner and it also remained above normal level (n=14, 36%; mean 1.0314 ± SD 0.5970; min 0.35 and max 2.25) in whole part of 2nd week with a descending manner. In this study, among the 61 patients with PACI, it shows serum d-dimer level mean was 1.0995 mg/L ± SD 0.5781 with maximum 2.54 and minimum 0.35. Serum d-dimer was moderately raised (n=24, 39%; mean 1.6175 ± SD 0.5648; min 0.85 and max 2.54) in early days of 1st week with a descending manner and it also remained above normal level (n=37, 61%; mean 0.7635± SD 0.2414; min 0.35 and max 1.55) in initial half and almost reach normal in later half of 2nd week. In this study, among the 44 patients with LACI, it shows serum d-dimer level mean was 0.3659 mg/L ± SD 0.1996 with maximum 0.70and minimum 0.01. Serum d-dimer was almost normal with early little rise (n=14, 32%; mean 0.5929; min 0.55 and max 0.70) in 1st week with a descending manner and it also remained within normal level (n=30, 68%; mean 0.26 ± SD 0.1471; min 0.01and max 0.56) throughout the 2nd week.

In this study, among the 18 patients with POCI, it shows serum d-dimer level mean was 0.4567 mg/L ± SD 0.2329 with maximum 0.75 and minimum 0.11. Serum d-dimer was almost normal with early little raise (n=12, 67%; mean 0.5525 ± SD 0.2004; min 0.11 and max 0.75) in 1st week with a descending manner and it also remained within normal level (n=6, 33%; mean 0.2650± SD 0.1732; min 0.12 and max 0.59) throughout the 2nd week.

In 2011 Young-Woo Park et al. mean D-dimer level at admission was 626.6 µg/L (range, 77-4,752 µg/L) and the mean level measured after seven days of treatment was 238.3 µg/L (range, 50-924 µg/L). Mean D-dimer level at admission was 215.3 µg/L in patients with focal infarctions, 385.7 µg/L in patients with multiple embolic infarctions, 566.2 µg/L in those with 1-19 cc infarctions, 668.8 µg/L in 20-49 cc infarctions, 702.5 µg/L in 50-199 cc infarctions, and 844.0 µg/L in >200 cc infarctions (p=0.044). On the 7th day of treatment, the D-dimer levels had fallen to 201.0 µg/L, 293.2 µg/L, 272.0 µg/L, 232.8 µg/L, 336.6 µg/L, and 180.0 µg/L, respectively (p=0.530) [9]. In 2010 SkoloudÃ-k D et al. a significant increase in the D-dimer levels was detected in patients with strokes of cardioembolic and atherothrombotic etiologies, and patients with occlusion of cervical or large intracranial arteries (P < 0.05) [10].

In 1993, Yamazaki M et al. in patients with cardioembolic stroke, D-dimer and alpha 2-antiplasmin-plasmin complex levels were higher during the acute and subacute phases, while thrombin-antithrombin III complex levels were higher during the acute phase than in patients with lacunar stroke and controls. In contrast, only D-dimer levels were higher in atherothrombotic stroke patients than controls during the acute and chronic phases and no significant alterations in these markers were observed in the patients with lacunar stroke[11].

In 2012 Tomoyuki Kono et al. concluded in acute ischaemic stroke, the cancer-associated ischaemic stroke is associated with elevated d-dimer and fibrin degradation products (n = 111, ÷2 = 67.21, P < 0.0001), even after controlling hypertension, hyperlipidaemia and advanced cancer (clinical stage IV) [12]. According to CotherHajatet al., risk factors between lacunar and non-lacunar infarct subtypes, atrial fibrillation was less prevalent in the lacunar (47 [17.5%]) than the non-lacunar group (139 [25.2%]) (P=0.01), and hypertension was more prevalent in the lacunar (173 [65.5%]) than the non-lacunar group (310 [57.4%]) (P=0.03). Risk factor profiles were similar between individual Bamford subtypes[13].In the multivariate model for non-lacunar versus lacunar infarct and individual Bamford subtypes versus lacunar infarct, Atrial fibrillation was independently associated with non-lacunar infarct (odds ratio [OR]=1.64; 95% CI, 1.08 to 2.50; P=0.02). When they compared individual Bamford subtypes versus lacunar infarct, atrial fibrillation was significantly more prevalent for TACI (OR=2.08; 95% CI, 1.22 to 3.54; P=0.007) and PACI (OR=1.83; 95% CI, 1.12 to 3.00; P=0.02) but not for POCI (OR=0.92; 95% CI, 0.48 to 1.74; P=0.9) [13]. In a study of 350 patients with first-ever acute ischemic stroke within 24 hours of their

symptoms, which lasted until entry, and who were admitted to the Department of Neurology, Toda Central General Hospital, from May 1994 to August 1999, it revealed no difference in background characteristics and risk factors among 4 clinical categories i. e. LACI, TACI, PACI, and POCI[14]. After multivariate analysis, higher D-dimer levels remained independently associated with cardioembolic stroke (p = 0.022) [15]. According to Tsuneaki et al., it showed that high D-dimer levels, CHF and history of stroke were associated with increased thromboembolic events[16].

Conclusion:

In this study, it shows that raised d-dimer (DD) was significantly associated total anterior circulation infarction (TACI) & partial anterior circulation infarction PACI and raised DD was significant differentiating point TACI or PACI from lacunar infarction (LACI) & posterior circulation infarction (POCI) (p value <0.0001) and raised D-Dimer might not differentiate between TACI & PACI (p value = 0.890).

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Bangladesh Journal of Neuroscience 2018; Vol. 34 (1): 32-38

Effect of Carbamazepine on Serum Cholesterol and Atherogenic Ratios in Young Adults with Epilepsy

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Abstract:

Background: *Epilepsy is a common chronic neurological disorder worldwide. Carbamazepine is one of the most commonly used antiepileptic drugs. It is a hepatic cytochrome P 450 enzyme inducer which is thought to cause alteration of serum lipids.* ***Objective:*** *To evaluate the effect of carbamazepine on serum cholesterol and atherogenic ratios in young adult epileptic patients.* ***Materials and methods:*** *This prospective study was conducted in the epilepsy clinic and Neurology OPD of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from December, 2017 to March, 2019. A total fifty seven newly diagnosed epileptic patients fulfilling the study criteria were studied. Serum TC, HDL-C, TG was measured by using Beckman Coulter-AU680 analyzer machine and LDL-C was calculated according to the Friedewald formula in the laboratory of Department of Biochemistry, BSMMU.* ***Results:*** *The mean (±SD) serum TC, LDL, TG, TC/HDL-C and LDL-C/HDL-C were significantly increased (p-value < 0.001) at 3 months of carbamazepine therapy in comparison to the baseline levels. The mean (±SD) serum HDL was decreased at 3 months of therapy which was not statistically significant (p-value: 0.135).* ***Conclusion:*** *Carbamazepine caused significant rise in serum TC, LDL-C, TG and atherogenic ratios (TC/HDL-C, LDL-C/HDL-C), and insignificant reduction in the serum HDL-C level after three months of therapy.*

Key words: *Epilepsy, Carbamazepine, Total cholesterol (TC), Low density lipoprotein cholesterol (LDL-C), High density lipoprotein cholesterol (HDL-C), Atherogenic ratio etc.*

Introduction:

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition[1]. It is considered to be one of the commonest and frequently encountered neurological conditions that impose the heavy burden on individuals, families, and also on healthcare systems. It is a global health care issue affecting about 50-70 million people worldwide and nearly 80% of cases live in the developing countries. The worldwide annual incidence and prevalence of epilepsy is 50 in 100 000 and 700 in 100 000, respectively. About 2.4 million people are diagnosed with epilepsy each year [2]. It is estimated that there are about 1.5 to 2.0 million epilepsy patients in Bangladesh[3]. Epileptic seizures are the result of excessive and abnormal cortical nerve cell activity in the brain[1].

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Seizure can be classified as generalized, focal and unknown onset [4]. The mainstay of treatment of epilepsy is antiepileptic drugs (AEDs). The choice of AEDs depends upon seizure type, epilepsy syndrome, comorbidities, other medications used, and the patient's age, lifestyle and socioeconomic conditions [5]. Carbamazepine (CBZ) is widely used as a drug of first choice in focal seizure and secondary generalized seizure [6]. It is a less costly, effective and well tolerated drug for seizure control in context of Bangladesh[7]. CBZ is metabolized in the liver. It induces hepatic microsomal cytochrome P450 enzymes, leading to alterations in the metabolism of bile acids, cholesterol, other lipids, bilirubins, and many other endogenous molecules and exogenous drugs[8]. The exact mechanism of alteration of serum cholesterol is not confirmed, but several possible mechanisms are conceivable. CBZ increases the activity of the hepatic cytochrome P450 system, which is involved in synthesis and metabolism of cholesterol[9]. CBZ might compete with the cholesterol in the utilization of hepatic cytochrome P450 enzymes, and this competition could lead to a reduction in the transformation of cholesterol in to bile acids. Thus, reduced cholesterol biotransformation increases total serum cholesterol levels[10]. CBZ also has marked protein-binding activity that typically causes reduced levels of Thyroxine (T_4) and free Thyroxine (FT_4). Reduced thyroxin level causes disinhibition of the rate limiting activity of HMG-CoA reductase, decrease LDL-receptor's activity, resulting in decreased catabolism of LDL and IDL. Thereby, serum total cholesterol, LDL-C levels are increased[11]. Therefore, the aim of the present study was to evaluate any alteration of the serum total cholesterol and atherogenic ratios in newly diagnosed young adult epileptic patients three months after carbamazepine therapy.

Materials and methods:

It was a longitudinal prospective study, conducted in the Epilepsy clinic of Department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka. Following a predefined protocol, a total seventy newly diagnosed young adult (19-40 years) epileptic patients of both sexes having focal or secondary generalized seizures were enrolled as study population. The patients were diagnosed by history, clinical examination, EEG and relevant investigations like CT scan / MRI of the brain. Their diagnosis was screened and supervised by concerned neurologists at epilepsy clinic. A semi-structured questionnaire was developed in English. Approval from the Institutional Review Board (IRB) of BSMMU was obtained prior to the commencement of this study. Atherogenic ratios were calculated as TC/HDL-C and LDL-C/HDL-C. Patients were started on carbamazepine at minimal effective dose 100mg 12 hourly and dose was titrated gradually upto the dose at which the seizure was controlled. Patients were informed about the possible common side effects of carbamazepine. Patients were monitored monthly for assessment of clinical response, any side effect of drug and drug compliance. Another fasting serum lipid profile was done at 3 months of CBZ therapy as per standard procedure. All other relevant investigations of all patients were done in the respective department of BSMMU, Dhaka. At the end of data collection, all the data were rechecked, coded and entered in the standard statistical software, data base using SPSS software (Version-25). Continuous variable was expressed as Mean ± SD. Categorical variable was presented by frequency and percentage. Paired student's t test was used to compare mean of various parameters of serum lipids at baseline and at 3 months of carbamazepine therapy. Unpaired t-test was used for comparison of changes of lipid parameters between male and female patients. The correlation of changes of parameters of serum lipids and atherogenic ratios with age, BMI, dose of carbamazepine was determined by the Pearson's correlation coefficient test. P value < 0.05 was considered as statistically significant. All statistical analysis was done by SPSS software windows version 25.

Results and observation

A total fifty-seven young adult patients fulfilling the inclusion and exclusion criteria were finally assessed in this study. The study results were as followed:

Table-I

Distribution of the study population according to different age range (n=57)

Age of patient /yrs	Total number	Percentage %
19 -25 yrs	30	52.6
26-30 yrs	16	28.1
31-40 yrs	11	19.3
Total	57	100.0
Mean±SDRange	25.7±6.1719 – 40	

Table I showing the mean age of the patients was 25.7 ± 6.17 years. The most frequent age group was 19-25 years representing 52.6% followed by 28.1% in 26-30 years.

Table-II

Distribution of the study population according to dose of carbamapezine at 3 months of therapy (n=57)

Dose	Frequency	Percentage (%)
<10 mg/kg/day	22	38.6
10-15 mg/kg/day	30	52.6
>15 mg/kg/day	5	8.8
Total	57	100.0
Dose (mg/kg/day) (Mean ±SD)	10.81±2.78	
Range	5.97 – 17.14	
Dose (mg/day) (Mean ±SD)	628.1±186.8	
Range	400 – 1200	

Table-III

Comparison of mean levels of serum TC, LDL-C, HDL-C, TG at baseline and at 3 months of carbamazepine therapy (n=57)

Parameter	Baseline(n=57) Mean±SD	At 3 months(n=57) Mean±SD	*P* value
TC (mg/dl)	147.2±22.1	163.1±25.4	<0.001^{s}
LDL-C (mg/dl)	82.2±20.5	96.8±23.1	<0.001^{s}
HDL-C (mg/dl)	46.6±6.6	45.0±8.2	0.135^{ns}
TG (mg/dl)	92.1±27.5	106.8±31.5	<0.001^{s}

Paired t-test was done as a test of significance and p-value <0.05 was considered as significant.s=significant, ns= non-significant

Table-IV

Comparison of atherogenic ratios at baseline and at 3 months of carbamazepine therapy (n=57)

Parameter	Baseline (n=57) Mean±SD	At 3 months (n=57) Mean±SD	*P* value
TC/HDL-C	3.19±0.61	3.73±0.81	<0.001^{s}
LDL-C/HDL-C	1.84±0.53	2.23±0.70	<0.001^{s}

Table-V

Correlation of age and BMI of patients; dose of carbamazepine at three months with percentage change of serum TC, HDL, LDL, TC/HDL, LDL/HDL.

Variables	Age		BMI		Dose (per kg/day)	
	r-value	p-value	r-value	p-value	r-value	p-value
Change of TC (mg/dl)	0.152	0.260	0.278[sn]	0.036	0.241	0.071
Change of HDL-C (mg/dl)	-0.016	0.903	0.172	0.200	-0.015	0.91
Change of LDL-C (mg/dl)	0.191	0.154	0.147	0.276	0.145	0.283
Change of TG (mg/dl)	-0.022	0.870	0.103	0.447	0.113	0.402
Change of TC/HDL	0.129	0.340	-0.001	0.991	0.095	0.482
Change of LDL-C/HDL-C	0.077	0.569	-0.064	0.636	0.088	0.513

Pearson's correlation coefficient test was done as a test of correlation. p- value< 0.05 was considered as significant, r- value signified the strength of correlation.

Discussion:

Carbamazepine is a commonly used antiepileptic drug in the treatment of focal and secondary generalized seizure. It is a hepatic microsomal enzyme inducer, and thought to alter the metabolism of lipids even in the early course of therapy. Several studies have reported significant increase in serum total cholesterol (TC) and LDL-C following carbamazepine therapy. But, the controversy regarding the influence of carbamazepine on serum HDL-C, and atherogenic ratios (TC/HDL-C, LDL-C/HDL-C) is still remained unsettled. However, the alteration in serum lipids may cause development of atherosclerotic vascular diseases in epileptic patients taking carbamazepine. This prospective longitudinal study was carried out in the epilepsy clinic, OPD of Neurology, BSMMU, Dhaka, with the primary aim to evaluate the effect of carbamazepine on serum cholesterol and atherogenic ratios in young adults with epilepsy. In this study, some demographic profile like age, sex, BMI of patients; seizure types; dose of carbamazepine and their correlation with the changes of different parameters of lipids were also assessed. In this study, seventy newly diagnosed or untreated epileptic patients fulfilling the study criteria during the study period (December, 2017 to March, 2019) were enrolled. However, thirteen of these patients did not return for follow-up visits, and the study was completed with fifty-seven patients. Among the thirteen dropped out patients, three developed mild hypersensitivity reaction in the form of itching, urticaria and discontinued the drug.A total fifty-seven young adult patients ranging from 19 to 40 years of age were finally assessed in this study. The mean (±SD) age of the patients was found to be 25.7 ± 6.17 years. It was observed that majority of the patients 30 (52.6%) were in 19-25 years age group. Mian et al., (2016)[3] conducted a study on demographic profiles of epileptic patients in Bangladesh, where they found that the most of the epileptic patients were younger (<30 years) in the study population. The mean age of case (uncontrolled seizure) and control (controlled seizure) groups were 21.84 ± 8.70 and 23.94 ± 10.28 years respectively. In this present study, among fifty-seven patients male were 36 (63.2%) and female were 21 (36.8%) and male female ratio was 1.7:1. It was observed that male were predominant among the epileptic patients which was 63.2% of the study population. Mian et al., (2016)[3] found that the male 31(62%) was predominant than female 19 (38%) among 50 Bangladeshi epileptic patients in case group. Aggarwal et al., (2009)[13] conducted a prospective study among 29 children where male were 16 (55%) and female were (45%). These studies were convenient to our current study in respect of sex. This present study showed that patients with focal to bilateral convulsive seizure (Secondary generalized seizure) was 35 (61.4%), focal seizure

with impaired awareness (complex partial seizure) was 13 (22.8%) and focal seizure with intact awareness (simple partial seizure) was 9 (15.8%). The seizure pattern of our study population was compatible with a previous study done by Habib et al., (2013)[7] in Bangladesh. Habib et al., (2013)[7] reported that among the patients with focal seizure 67% was secondary generalized seizure, 22% was complex partial seizure and 11% was simple partial seizure. In the present study, the mean (± SD) dose of carbamazepine at three months was 10.81 ± 2.78 mg/kg/day (628.1 ± 186.8 mg/day). The maximum patients 30 (52.6%) took carbamazepine at a dose of 10-15 mg/kg/day. The 38.6% of patients took carbamazepine at a dose of < 10 mg/kg/day, whereas only 8.8% of patients got carbamazepine at > 15mg/kg/day. The daily dose of carbamazepine ranged 400-1200 mg/day (5.97 – 17.14 mg/kg/day). The dose of CBZ was compatible to the mean dose (10.3 ± 1.1 mg/kg/day) in a previous study done by Aggarwal et al., (2009)[13]. In another case-control study conducted by Aggarwal et al., (2004)[14] the mean dose of CBZ was 13.1 ± 3.5 mg/kg/day. These studies were compatible with the current study in respect of dose of carbamazepine.In this current study the baseline levels of serum TC, HDL-C, LDL-C, TG and atherogenic ratios (TC/ HDL-C, LDL- HDL), were compared to their levels at 3 months of CBZ therapy. Results showed that mean (±SD) serum TC at baseline was 147.2 ± 22.1 mg/dl and at 3 months after carbamazepine therapy was 163.1 ± 25.4 mg/dl. A significant increase in serum TC was found (p- value <0.001) at 3 months of treatment in comparison to baseline level. The mean (±SD) serum LDL-C was significantly increased from 82.2 ± 20.5 mg/dl to 96.8 ± 23.1 mg/dl (p-value <0.001). These results were supported by several studies done around the world such as Aggarwal et al., (2009)[13], Mahmoudian et al., (2004)[15], Bramswig et al., (2003)[12].Bramswig et al., (2003)[12] showed that TC and LDL-C levels significantly increased from 190 ± 30 mg/dl to 209 ± 25 mg/dl (p < 0.006) and from 126 ± 27 mg/dl to 142 ± 25 mg/dl (p < 0.011), respectively. Aggarwal et al., (2009)[13] found that the mean (±SD) serum TC significantly increased from baseline 130.6 ± 27.3 mg/dl to 144.7 ± 32.9 mg/dl at three months of therapy (p-value < 0.018). The LDL-C was also significantly increased from 72.3 ± 24.6 mg/dl to 86.6 ± 30.6 mg/dl (p-value < 0.016). These findings were convenient to our present study. In this study, the mean (±SD) serum TG level was 92.1 ± 27.5 mg/dl and 106.8 ± 31.5 mg/dl at baseline and at 3 months respectively. Serum TG levels increased significantly after carbamazepine therapy in comparison to the pretreatment levels (p- value < 0.001). Bramswig et al., (2003)[12] reported the significant rise of mean serum TG from 95 ± 39 mg/dl at baseline to 107 ± 37 mg/dl at three months of therapy (p-value < 0.025) which supported the present study result. Regarding the changes of serum HDL level, this current study showed that mean (±SD) serum HDL levels were 46.6 ± 6.6 mg/dl and 45.0 ± 8.2 mg/dl at baseline and at 3 months respectively. The mean HDL-C level reduced at 3 months after carbamazepine therapy in comparison to baseline level which was statistically not significant (p-value: 0.135). This study result was compatible to a study conducted by Aggarwal et al., (2009)[13], where the mean HDL-C level was 44.3 ± 15.1 mg/dl and 42.2 ± 13.0 mg/dl at baseline and at three months respectively. The decreased level of HDL-C was not statistically significant (p-value: 0.243). Nikolaos et al., (2004)[10] conducted a case control study among adults showing a significantly (p-value <0.001) higher HDL-C (57.8 ±5.0 mg/dl) in CBZ group than control group (52.4 ± 6.8 mg/dl). These contradictory study results might be due to different study design, age, dietary habits, racial factor and duration of carbamazepine therapy. There were very few prospective studies, whereas most of the studies were cross sectional and a variety of different control groups were used for comparison. Regarding the changes in atherogenic ratios (TC/HDL, LDL/HDL) the present study showed significant increase (p-value < 0.001) in the mean (±SD) of TC/HDL and LDL/HDL. The mean (±SD) of TC/HDL at baseline and at 3 months were 3.19 ± 0.61 and 3.73 ± 0.81 respectively. The mean (±SD) of LDL-C/HDL-C were 1.84 ± 0.53 and 2.23 ± 0.70 at baseline and at 3 months respectively. This study result was supported by previous studies

conducted by Aggarwal et al., (2009)[13], Mahmoudian et al., (2005)[15]. Aggarwal et al., (2009)[13] showed that the mean± (SD) TC/HDL significantly (p-value-0.001) increased from 3.1 ± 0.86 at baseline to 3.7 ± 1.1 at 3 months of therapy. That study also revealed significant rise (p-value < 0.018) of mean LDL/ HDL from 1.8 ± 0.7 at baseline to 2.2 ±0.9 at three months of therapy. The present study showed that there was no significant correlation of changes of TC, LDL-C, HDL-C, TG and atherogenic ratios (TC/HDL-C, LDL-C/HDL-C) with age, sex, BMI and dose of carbamazepine. Nikolaos et al., (2004)[10] reported no significant correlations between changes in serum lipid levels and age, sex, BMI of the epileptic patients, which was convenient to the current study. The mean changes of TC, LDL-C, HDL-C, TG and atherogenic ratios between male and female were not significantly different. The mean (±SD) changes of TC and TG in female were greater than male which was not statistically significant (p-value: 0.951, 0.259).The correlation of changes of cholesterol and atherogenic ratios with the dose of carbamazepine were not significant in this present study. Several studies like Bramswig et al., (2002)[16], Aggarwal et al., (2009)[13] also found no significant correlation of changes of parameters of serum lipids with dose and plasma concentration of carbamazepine which was convenient to the results of current study. The present study revealed that carbamazepine caused significant rise of serum TC, LDL, TG levels and atherogenic ratios (TC/HDL-C, LDL-C/HDL-C) at three months of therapy. The reduction of serum HDL-C at three months of therapy was not significant. There was no significant correlation of age, sex, BMI of patients and dose of carbamazepine with the changes of serum cholesterol and atherogenic ratios at three months of therapy. The present study revealed that carbamazepine caused significant rise of serum TC, LDL, TG levels and atherogenic ratios (TC/HDL-C, LDL-C/HDL-C) at three months of therapy. The reduction of serum HDL-C at three months of therapy was not significant. There was no significant correlation of age, sex, BMI of patients and dose of carbamazepine with the changes of serum cholesterol and atherogenic ratios at three months of therapy.

Conclusion:

The present study revealed that carbamazepine caused significant rise of serum TC, LDL, TG levels and atherogenic ratios (TC/HDL-C, LDL-C/HDL-C) at three months of therapy. The reduction of serum HDL-C at three months of therapy was not significant. So, those patients who are taking carbamazepine are prone to develop dyslipidemia, even in the early course of treatment.

Limitations:

Our study was done in short period, with a small sample size. Serum carbamazepine level was not measured, and the correlation of serum carbamazepine level with the changes of lipid parameters could not be evaluated.

Recommendations:

Patients taking carbamazepine should be warned about the possibility of developing dyslipidemia, and dyslipidemia associated cardiovascular and other atherosclerotic diseases. Lipid profile should be monitored routinely during carbamazepine therapy in epileptic patients. Pharmacological and non-pharmacological measures including adequate dietary advice, regular exercise can be suggested to avoid dyslipidemia. Further studies can be conducted to solve the controversy regarding the alteration of HDL-C level and the exact mechanism.

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Bangladesh Journal of Neuroscience 2018; Vol. 34 (1): 39-44

Presence of Herpesviridae Genome in CSF of GBS Patients

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Abstract:

Background: *Guillain Barre Syndrome (GBS) is considered as an immune mediated inflammatory disease of peripheral nerves and nerve roots. Herpes viruses like CMV, EBV, HSV and VZV infections are associated with GBS. The aim of the study was to identify the presence and frequency of different Herpes virus genome by PCR assay in CSF of GBS patients* ***Methods:*** *An observational, cross sectional study was carried out in the Department of Neurology, BSMMU, and Dhaka. A total 50 (fifty) admitted GBS patients were included after fulfilling the inclusion and exclusion criteria. About 2 ml of CSF was taken for detection of viral nucleic of CMV, EBV, HSV1, HSV2, VZV and HHV6 by Multiplex PCR method.* ***Results****: Herpesviridae genome in CSF of study population was present in 9 (18%) patients. Maximum 3 (33.3%) cases were HSV1, EBV and HSV2 found in 2 (22.2%) patients, CMV and VZV in 1 (11.1%) patient respectively. AMAN (66.6%) was the most frequent electrophysiological pattern; followed by AIDP (33.3%), mean CSF protein was (159±81) mg/dl and mean cell count was (2±3)/cmm in these patients. Herpes virus genome positive group patients were more disabled and received definitive treatment more than the others.* ***Conclusion:*** *Herpesviridae genome was present in CSF of GBS especially in early collected CSF sample. Antiviral drugs might have a role in treating GBS patients having Herpes virus genome in CSF.*

Key words: *Guillain Barre Syndrome (GBS), Herpes Virus genome, PCR, CSF.*

Materials and methods:

This cross sectional observational study. It was conducted in department of Neurology (In patient department), BSMMU, Dhaka. Male and female of 18 years or above who were diagnosed clinically by accepted clinical criteria as Guillain-Barre syndrome in inpatient department, department of Neurology, BSMMU, Dhaka was taken as study population. About 2-3 ml of CSF was taken for detection of PCR for viral nucleic acid of six virus of Herpesviridae group (CMV, EBV, HSV1, HSV2, VZV, and HHV6) by Multiplex PCR method (Seeplex meningitis ACE kit) in Microbiology department of BSMMU. Pattern of clinical presentationwas documented and disability was graded by Hughes functional grading scale. Routine CSF study was done in the Biochemistry and Clinical Pathology department for CSF protein and cytology respectively. Nerve conduction study was performed in the "Neurophysiology laboratory" of BSMMU and pattern of findings of these investigations were recorded. Presence and frequency of different Herpes virus genome was expressed in percentage and their association with variation in clinical presentation, electro-physiological findings and routine CSF findings was statistically analyzed by Chi-square test and t- test. The P value <0.05 was considered statistically significant.

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Results and observations:

Table-I

Distribution of study population by age in relation to Herpesviridae genome in CSF (n=50)

Age in years	CSF viral genome by PCR			P-Value
	Absent n (%)	Present n (%)	Total n (%)	
< 20	3 (7.3)	3(33.3)	6 (12)	0.029 s
21- 30	13(31.7)	4(44.4)	17 (34)	0.465 ns
31- 40	9 (22)	0 (0)	9 (18)	0.120 ns
41- 50	6 (14.6)	0 (0)	6 (12)	0.221 ns
>50	10(24.4)	2(22.2)	12 (24)	0.890 ns
Total	41 (100)	9 (100)	50 (100)	0.098 s

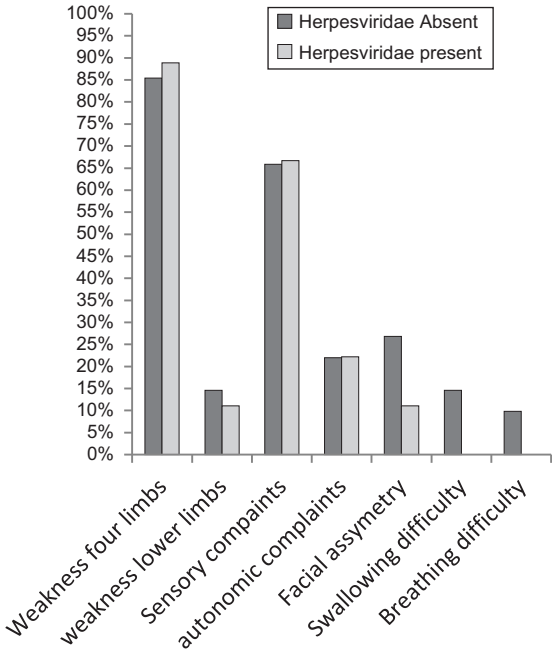

Fig.-1 (Bar diagram): *Presenting complaints of study population.*

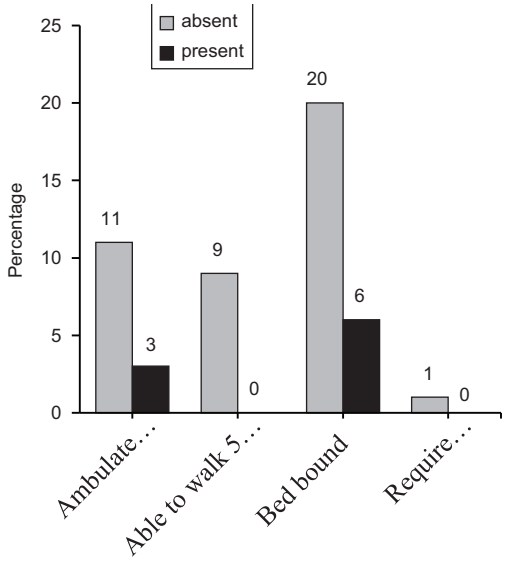

Fig.-2 (Bar diagram): *Disability status of study population.*

Table-II

Presence of Herpesviridae genome in CSF of study population (n=50)

Name of the Herpes virus	Number	Percentage
CMV	01	11.1
EBV	02	22.2
HSV 1	03	33.3
HSV 2	02	22.2
VZV	01	11.1
HHV 6	00	0.00
Total	09	100

Table-III

CSF protein level of study population (n=50)

	Absent Group CSF protein (mg/dl)	Present Group CSF protein (mg/dl)	Total	P-Value
Mean	178	159	175	0.774
Standard Deviation	195	81	179	

Table-IV:

CSF cytology of study population (n=50)

	Absent Group (CSF cell/cmm)	Present Group (CSF cell/cmm)	Total	P-Value
Mean	12	2	10	0.523
Standard Deviation		47	3	42

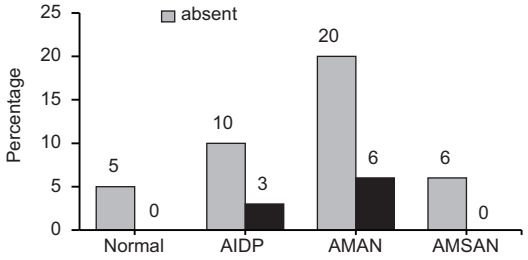

Fig.-3: *(Bar diagram): Electrophysiological pattern of study population*

Table-V

CSF collection time to detect Herpesviridae genome among cases at time interval in weeks (n=50)

CSF collection time	CSF viral genome by PCR			
	Absent n (%)	Present n (%)	Total n (%)	P-Value
< 7 days	0 (0)	1(11.1)	1 (2)	0.031 ^{s}
8-14 days	22(53.7)	7(77.8)	29 (58)	0.184 ^{ns}
15-28 days	19(46.3)	1(11.1)	20 (40)	0.050 ^{ns}
Total	41 (100)	9 (100)	50(100)	0.023 ^{s}

Table-VI

Distribution of study population by received treatment (n=50)

Treatment modalities	CSF viral PCR positivity			
	Absent n(%)	Present n(%)	Total n(%)	P-Value
Conservative	29 (70.7)	4(44.4)	33 (66)	0.131 ^{ns}
Plasma exchange	9 (22)	5(55.6)	14 (28)	0.042 ^{s}
IVIG	3 (7.3)	0 (0)	3 (6)	0.402 ^{ns}
Total	41 (100)	9 (100)	50 (100)	0.110 ^{ns}

Discussion:

Guillain-Barre Syndrome (GBS) is considered as an immune mediated inflammatory disease of peripheral nerves and nerve roots. Two thirds of patient has a preceding history of various viral and bacterial infections before the symptoms onset[1]. GBS is thought to be result of immune reaction against these infectious agents having epitope similar to peripheral nerves myelin sheath or axonal membrane component. This type of molecular mimicry was found mainly those of bacterial infectious agent like Campylobacter jejuni, Hemophylus influenzae and Mycoplasma. Herpes viruses like CMV, EBV, HSV and VZV infections are associated with GBS[3]. The above mentioned mechanism of nerve injury cannot be proved in virus associated GBS patients who may have different pathogenesis described in some study.

Different study shows that antibody against herpes virus and PCR for herpes virus genome was found in serum and CSF of GBS patients. As their study found PCR for Herpes virus genome was present in CSF of GBS patients after disease onset so they claimed that there may be ongoing infection or presence of Herpes virus genome in CSF has a different role in GBS pathogenesis. This cross-

sectional observational study was carried out primarily with an aim to identify the presence of different Herpes virus genome by multiplex PCR method in CSF of GBS patients, to identify their frequency, any association with variation in clinical presentation, electrophysiological pattern and routine CSF findings of them. A total 50 (fifty) GBS patients admitted in the Neurology department of BSMMU, Dhaka, were included after fulfilling the inclusion and exclusion criteria. GBS patients of any age and sex were included in our study.

We have made two groups on the basis of presence or absence Herpes virus genome in CSF of GBS patients within 4 weeks of disease onset. We have also compared between two groups to find out any association of CSF Herpes virus genome positivity with any variation in pattern of clinical presentation, electrophysiological findings, cytological and biochemical parameter of CSF. The timing of presence of Herpes virus genome by multiplex PCR method in CSF of GBS patients and its significance was also observed.

Analysis of age distribution (Table-I) of two groups showed that the mean age (±SD) was 39 (±15) years in CSF Herpes virus genome absent group and 30 (±16) years in CSF Herpes virus genome present group. Male patients were 42 (84%) and female patients were 8 (16%). Higher frequency was found in male than female. Most of the study patients were young adults of 21-30 yrs, 4 (44.4%) patients in CSF Herpes virus genome positive group and 13 (31.7%) patients in CSF Herpes virus genome negative group. So our study showed that Herpes virus genome in CSF is found in younger GBS patients. In this study presenting complaints (Figure-1, Bar diagram) was weakness of all four limbs in 43 (86%) patients, lower limb weakness in 7 (14%) patients. Sensory complaints were present in 33 (66%) of patients. Complaints of facial weakness or deviation were present in 12 (24%) patients, 4 (8%) patient had breathing difficulty and 6 (12%) patients had dysphagia. There was no significant difference found in terms of clinical presentation in between two groups. In our study maximum number of patients 20 (48.8%) were in the grade 4 disability scale in Herpes virus genome absent group and 6 (66.7%) patients were in Herpes virus genome present group. Patients who had Herpes virus genome in CSF were more disabled during admission than who had absent Herpes virus genome in CSF (Figure-II). Our study found Herpes virus genome in CSF was present in 9 (18%) patients and was absent in 41 (82%) patients. Maximum 3 (33.3%) cases were HSV1 followed by 2 (22.2%) cases were EBV and HSV2, 1 (11.1%) was CMV and VZV respectively (Table-II). This result has similarity with that of Armin S. et al., (2014)[13] who found Herpes virus genome in CSF of GBS patients in 20% cases (3 out of 15 patients).

In our study CSF was drawn between 8-14 days of disease onset in maximum 22 (53.7%) patients followed by 19 (46.3%) patients within 15-28 days in CSF Herpes virus genome negative group. In contrast CSF was drawn between 8-14 days of disease onset 7 (77.8%) patients and 1 (11.1%) patient within 7 days in CSF Herpes virus genome positive group. So our study found that Herpesviridae genome was found more in GBS patients whose CSF was taken early after disease onset (Table-V). Our one specific objective was to find out any correlation between two groups in regards of CSF findings. Mean protein was (178±195) mg/dl in Herpes virus genome absent group and (159±81) mg/dl in Herpes virus genome present group respectively. Mean cell count was (12±47)/cmm in Herpes virus genome absent group and (2±3)/cmm in Herpes virus genome present group respectively (Table-III). No significant difference was found between two groups but CSF cell count and protein was higher in Herpesviridae genome negative group (Table-IV).

We also had a specific objective to see association of presence of Herpes virus genome in CSF with electrophysiological pattern of our patients. The present study found predominant electro-physiological subtype in both group was AMAN found in 6 (66.7%) patients in Herpes virus genome positive group and 20 (48.8%) patients in CSF Herpes virus genome negative group. Next common electrophysiological pattern was AIDP observed in 3 (33.3%) patients in CSF Herpes virus genome positive group and 10 (24.4%) patients in CSF Herpes virus genome negative group

respectively. NCS was normal in 5 (12%) patients (Figure-III). No significant association was found between presence of Herpes virus genome in CSF and electrophysiological pattern. But axonal variants (AMAN and AMSAN) constitute the predominant subtype 64% (52% AMAN and 12% AMSAN) in our population. A study done by Islam et al. (2010)[7] in Bangladesh, also found higher frequency of axonal variants in 67% (AMAN-56% and AMSAN-11%) followed by AIDP in 22% of cases and 11% were unclassified. Thus the present study has similarities with the previous study although AIDP was the predominant subtype in many developed countries including Europe and North America. Another observation of our study is presence of CSF Herpes virus genome render the patient to receive more specific treatment than who has absent Herpes virus genome in CSF. Definitive treatment was given more in CSF Herpes virus genome positive group (55.6%) patients than CSF Herpes virus genome negative group (49.3%) patients. Fourteen (14, 28%) patients were treated with plasma exchange and 3 (6%) patient received intravenous immunoglobulin during their course of illness. Majority 33 (66%) of patients had received conservative treatment (Table-VI).

Conclusion:

The present study showed that Herpesviridae genome may be found in CSF of GBS patients after the disease onset especially in younger patients. The presence of Herpes virus genome by PCR assay in CSF of GBS patients early in the disease course carries significance. It may be related with ongoing or current infection or a different pathogenesis may coexist in these GBS patients but actual mechanism of Herpesviridae genome presence in CSF yet to be elucidated. Present study also showed that Herpes virus genome positivity was associated with greater disability of the GBS patients and necessitated specific costly treatment more than the other patients. But present study failed to correlate the presence of Herpesviridae genome in CSF of GBS patients with routine CSF findings and with the electrophysiological pattern. As our study showed that early in the disease course of GBS patients Herpesviridae genome is present in CSF, so whether antiviral drug can be effective or not in these patients is a matter of debate and demand for further study

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Bangladesh Journal of Neuroscience 2018; Vol. 34 (1): 45-51

Study of Etiological Pattern of Acute Meningo-Encephalitis Syndrome

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Abstract:

Background: *Acute meningo-encephalitis syndrome is a medical emergency which claim urgent management. So the objectives of the present study was to find out aetiological factors and differentiating parameter between different types acute meningo-encephalitis syndrome with minimum investigation.* ***Methods:*** *This hospital based observational study was carried out in medicine units of Chittagong Medical College. Fifty cases were studied who present with acute onset fever with central nervous system dysfunction.* ***Results:*** *In this study it reveals that hospital rate of bacterial meningitis was 26%, viral encephalitis was 34% and severe malaria was 26% among the patient with acute meningo-encephalitis syndrome. It shows that mean age (years) in viral encephalitis was 33.71, bacterial meningitis was 34.15 & in severe malaria was 27.92. It reveals that all patients of this series presented with acute onset fever (n=50,100%), maximum patients present with sign of meningeal irritation (n=44, 88%) & altered mental state (n=41,82%). Few patients was present with new onset seizure (n=11,22%) & neurologic deficit (n=1,2%). In Bacterial meningitis most patient was with low CSF glucose (n=10, 76.9%). In viral meningitis there were normal CSF glucose level (n=17,100%). High protein content in bacterial (n=13,100%) & Viral (n=15,88.2%) was found. It shows differential count of CSF WBC in different type of meningitis where in Bacterial meningitis it is neutrophils & in other type of meningitis it is the lymphocyte.* ***Conclusion****: CSF findings are hallmark of diagnosing various type of meningitis. CSF glucose and protein content found in this study significantly correlate with different etiology (p value = 0.000).*

Key word: *Acute, Meningo-encephalitis, Viral, Bacterial, Malaria*

Introduction:

Acute meningo-encephalitis syndrome is defined as acute onset fever with altered mental state or new onset seizure or with sign of meningeal irritation and neurologic deficit[1,2]. The most common types of acute meningitis are acute bacterial meningitis (70%) with incidence of 2.5 cases per 100000 population per year and aseptic meningitis (30%)[1,3]. Acute bacterial meningitis is a severe illness characterized by purulent CSF[1]. Aseptic meningitis is milder and typically self-limited, usually caused by viruses but sometimes by bacteria, fungi, parasites or non-infectious inflammation in systemic lupus erythomatosus, Behcet's disease, Sarcoidosis, malignancy & Mollaret meningitis with HSV-2[2,3]. In adult bacterial meningitis causative organism are Streptococcus pneumonia (~50%), Neisseria (~25%), Group-B streptococcus / S.agalactae (~15%), listeria (~10%), Haemophillus (<10%) and among virus 75-90% cause is HSV-2 & Arbo virus[1,3].

Many cases of infectious meningitis begin with a vague prodrome of viral fever. The classic meningitis triad of fever, headache and nuchal rigidity develops over hours or days. Brudzinski's and kernig's sign may also positive. According to Thomas KE et al, diagnostic accuracy of signs of meningeal irritation in patients with suspected meningitis showed nuchal rigidity, Kernig's sign & Brudzinski's sign sensitivity 30%, 5% & 5%, specificity 68%, 95% & 95%, positive predictive value 26%, 27% & 27%, negative predictive value 73%, 72% & 72%, positive likelihood ratio 0.94,

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0.97 & 1.0 and negative likelihood ratio 1.02, 1.0 & 0.97 respectively[11,12]. Meningococcal infection is associated with skin rash in 70% cases.[2,5] Although brain parenchyma is not typically involved early in meningitis. Lethargy, confusion, seizures and focal deficits may develop, particularly in untreated bacterial meningitis[3,4].

Acute meningitis is a medical emergency (mortality 20%, recovery rate with antibiotic 30%) [1]. So it requires a rapid diagnosis and treatment. After IV access and blood cultures are obtained lumbar puncture is done to obtain CSF for Gram stain, culture, cell count and differential and glucose and protein content. In bacterial meningitis CSF shows Polymorphnuclear pleocytosis in 90% cases, decreases glucose in 60% cases ,increased protein in 90% cases, increased pressure in 90% cases & in viral meningitis CSF pleocytosis in >95% cases[1-4].

Sometimes other investigation is needed to exclude cerebral malaria, metabolic, vascular & toxic causes of coma, electrolyte imbalance, organ failure, septicaemia & ICSOL. These tests must be done as rapidly as possible. However, patients with signs with mass effect (e.g, focal deficits, papilloedema, deterioration in consciousness, seizures) require head CT before lumber puncture because lumbar puncture can result in a shift of intracerebral contents downwards, towards and into the spinal canal. This process is known as coning, and is potentially fatal[5].

Recently CSF C-reactive protein with latex particle use in differentiating bacterial and non-bacterial meningitis & identification of a CSF inhibitors of macrophage Listecidal function as Interleukin-10.[35-37] Gram (-)ve bacterial meningitis 100% positive for Limulus amebocyte Lysate assay with the possibility of false positive result[3]. The best single test to differentiate bacterial meningitis from viral is rise of CSF lactic acid level (<2mmol/L in viral, 2-6mmol/L in partially treated case & >6 mmol/L in bacterial etiology).A normal CSF Lactic acid level could have eliminate need for unnecessary repeated lumbar puncture & also eliminate the need of empirical antibiotic coverage pending CSF culture result[5].

Methods:

It was an observational study done in the Medicine Department of Chittagong Medical College, Chittagong, Bangladesh among 50 cases suspected meningoenchephalitis during a period of one year. Patients who have history of fever less than 14 days and, and patients presented with one or more of the followings:- new onset seizure, altered mental state like coma, lethargy, confusion or agitation, neurologic deficit like focal sign of weakness, abnormal gait, involuntary movement or abnormal posture or abnormal tone of muscle, sign of meningeal irritation like nuchal rigidity, Brudzinski's sign or Kernig's sign and patient/Party who willing to take part in the study were included in the study and patients age <13yrs and patient who present with simple febrile seizure were excluded. All data were collected in individual case record form. This was done by taking history from patients or his or her attendants. All the cases were clinically examined including fundoscopy and then some routine first line investigation sent for all patients and second line investigation for selective cases. When there was sign of raised intracranial pressure (e.g, deterioration of level of consciousness with bradycardia, hypertension, irregular respiration, dilated poorly reacting pupils, sixth nerve palsy, decerebrate posture, papilloedema) brain imaging was done prior to Lumbar puncture.

All patients was managed properly and due nursing care (eg, management of unconscious patient) provided by duty nurse. All Lumbar puncture were done by duty doctors of medicine ward, examined in pathology & microbiology department of Chittagong Medical College and all Blood film for malarial parasite was done in Malarial Research Laboratory, CMC. Data was coded, edited and entered into computer and were analysed by using SPSS 12 and presented with tables, graphs keeping in view the objective of the study.

Results:

Table-I

Distribution of patients in relation with diagnosis among the patient of acute meningo-encephalitis syndrome (n=50).

	Viral encephalitis	Bacterial meningitis	Severe malaria	Not diagnosed
No of patient	17	13	13	7
%	34	26	26	14

It shows that in cases of acute meningo-encephalitis syndrome, viral encephalitis was 34%, bacterial meningitis 26%, severe malaria 26% & 14% cases there were no diagnosis.

Table-II

Distribution of patients in relation with age (n=50).

		Viral encephalitis	Bacterial meningitis	Severe malaria	Not diagnosed
Age (year)	Mean	33.71	34.15	27.92	47.29
	Range	17-55	19-48	18-38	38-55
	SD	12.282	8.952	7.729	6.726

It shows that mean age (years) in viral encephalitis was 33.71, bacterial meningitis was 34.15 & in severe malaria was 27.92.

Table-III

Distribution of patients in relation with CSF glucose level (n=50)

Diagnosis	CSF glucose(mg/dl)		Total
	Low(<40mg/dl)	Normal(≥40mg/dl)	
Viral meningo-encephalitis	0	17	17
Bacterial meningitis	10	3	13
Severe malaria	0	13	13
No diagnosis	2	5	7

It shows CSF glucose concentration among different types of meningitis. In Bacterial meningitis most patient was with low CSF glucose (n=10, 76.9%). In viral meningitis there were normal CSF glucose level (n=17,100%).

Table-IV

Distribution of patients in relation with CSF protein level (n=50).

Diagnosis	CSF protein(mg/dl)		Total
	normal(<45mg/dl)	Raised(≥45mg/dl)	
Viral meningo-encephalitis	2	15	17
Bacterial meningitis	0	13	13
Severe malaria	11	2	13
No diagnosis	7	0	7

It shows CSF protein content among different type of meningitis. High protein content in bacterial (n=13,100%) & Viral (n=15, 88.2%).

Table-V

Correlation of different clinical feature with viral, bacterial & malarial causes of acute meningo-encephalitis syndrome using one way ANOVA.

		Sum of Squares	Df	Mean Square	F	Sig.
Gender	Between Groups	.008	2	.004	.015	.985
(male=1,)	Within Groups	10.271	40	.257		
female=2	Total	10.279	42			
Age category	Between Groups	1.991	2	.996	1.057	.357
(13-25=1, 26-35=2,	Within Groups	37.683	40	.942		
36-45=3,>45=4)	Total	39.674	42			
CSF protein	Between Groups	5.613	2	2.806	32.472	.000
(Normal<45mg/dl,	Within Groups	3.457	40	.086		
Raised ≥45mg/dl)	Total	9.070	42			
CSF glucose	Between Groups	5.367	2	2.683	46.512	.000
(Normal ≥40mg/dl,	Within Groups	2.308	40	.058		
Low <40mg/dl)	Total	7.674	42			
CSF WBC	Between Groups	6.494	2	3.247	76.744	.000
(Normal upto 5,	Within Groups	1.692	40	.042		
Raised>5/mm^3)	Total	8.186	42			

It shows there is CSF protein, CSF glucose & CSF WBC category significant difference of between viral, bacterial & malarial causes of acute meningo-encephalitis syndrome and p value respectively .000, .000 & .000. It also shows gender & age category were not differentiating criteria between viral, bacterial & malarial causes of acute meningo-encephalitis syndrome p value > 0.05.

Discussions:

Infection of central nervous system is a medical emergency. The incidence of bacterial meningitis is more than 2.5 per 100,000 people per year[3].The exact incidence of viral meningitis is very difficult to determine since most cases go unreported to public health authorities. There is no exact record yet in our country. About 400 patients admitted with meningitis in CMCH in medicine unit per year[6].

In this study, among the 50 patients with acute meningo-encephalitis syndrome, viral encephalitis was found 17 (34%), bacterial meningitis were reveals 23 (26%) severe malaria were found 13 (26%).In this study it was explored that severe malaria is an important cause among the patients with acute meningo-encephalitis syndrome since Chittagong is a malaria endemic zone.

A hospital-based study at Dhaka Medical College Hospital, Mymensingh Medical College Hospital, MAG Osmani Medical College Hospital, Rajshahi Medical College Hospital from June 2003 to July 2005 to investigate the etiologies of bacterial meningitis in Bangladesh were diagnosed with bacterial meningitis 136 (18%)[7].

In another prospective, hospital-based study to define the causes of encephalitis among patient admitted to Dhaka, Mymensingh and Rajshahi Medical College Hospitals in Bangladesh during 2003, viral encephalitis was found 25 (37.7%), bacterial meningitis was found 22 (34.9%)[8].

In study of consecutive patients (age's e"16) with aseptic meningitis or encephalitis treated in Turku University Hospital, Finland, during 1999 to 2003 where etiologic diagnosis was achieved by PCR were showing 43% of the patients with meningitis and 17% of those with encephalitis[9].

In this study, among the 50 patients with acute meningo-encephalitis syndrome, it shows there were an overall male preponderance with a male to female ratio was 1.6:1 (male=31,female=19).It also shows that mean age (years) in viral encephalitis was 33.71, bacterial meningitis was 34.15 & in severe malaria was 27.92.It reveals that maximum patients (n=29,58%) were between 26-35 & 36-45 years of age and all age groups were equally affected considering age less than 13 as an exclusion criteria.

According to Ridwanur Rahman, et al.,cerebral malaria was common for all the age group & highest mortality was found among the 51-60 age group[10].

A study at King George Hospital, India from June 2003 – December 2006, all patients with abnormal CSF findings were reviewed where 'meningitic' cases occurred in young immunocompetent patients aged between 17-32 years[11].

In this study, among the 50 patients with acute meningo-encephalitis syndrome, it reveals that average duration (days) before presentation in different type of acute meningo-encephalitis. In case of viral encephalitis it was 3.35 (1-6), bacterial meningitis 3.23 (1-6) & severe malaria 3 (1-5) & the area of the box also represent the no. of cases in individual category.Allthe patients of this series presented with acute onset fever (n=50,100%). Most of the patients presented with sign of meningeal irritation (n=44, 88%), altered mental state (n=41,82%). It also reveals that patients were presented with nuchal rigidity (n=39, 78.0%), Kernig's sign 24, 48.0%) & with confusion (n=22, 44.0%). Few patients was presented with new onset seizure (n=11, 22%), lethargy (n=11, 22.0%), coma (n=8, 16.0%), Brudzinski's sign (n=6, 12.0%), agitation (n=1, 2.0%) & abnormal tone (n=1, 2.0%). In this series no patient was presented with focal sign of neurologic deficit, abnormal gait, and involuntary movement.

A study of 104 cases of cerebral malaria (73 male, 31 female between July 1995 to June 1996 in Chittagong Medical College Hospital, revealed intermittent fever (83%), vomiting (80%), headache (75%), convulsion (60%) and history of travel or residence in malaria endemic area were important features noted in patients with cerebral malaria.[50] Most of the patients (69%) were admitted within 25 to 48 hours following unconsciousness[10].

A study in sixty-eight parasitologically-confirmed adults admitted to the Chittagong Medical College Hospital showed the duration of present illness (6.96±3.24 days) before hospitalization and the duration of severe illness (2.31±1.96 days) were longer among those who died than among survivors[12]. In Thomas KE et al study in the diagnostic accuracy of Kernig's sign, Brudzinski's sign and nuchal rigidity in adults with suspected meningitis showed nuchal rigidity was present in 30% and Kernig's or Brudzinski's sign only in 5% cases of adults with meningitis[13].

In Raschilas F, Wolff M, Delatour F, et al multycentric study in outcome of and prognostic factors for herpes simplex encephalitis in adult patients showed eighty five (91%) of 93 adults with HSV-1 encephalitis were febrile on admission,14 disorientation (76%), speech disturbances (59%) and behavioral changes (41%) were the most common features, and one third of patients had seizures[14]. In a study in King George's Medical College, Lucknow, India on clinical features & prognostic indicators of Japanese encephalitis in children, a high incidence of fever (94.5%), coma (100%) and convulsions (84.7%) was seen. Focal neurological deficit was found in 29.3 per cent of patients and pleocytosis in the cerebrospinal fluid in 32.3 per cent. An extrapyramidal syndrome developed in 21.3 per cent patients during the convalescent stage[14].

In this study, among the 50 patients with acute meningo-encephalitis syndrome, it shows that mean CSF glucose (mg/dl) in viral encephalitis was 64.71,bacterial meningitis was 38.92 & in severe malaria was 66.85.Most of the patients with bacterial meningitis 10 (76.9%) revealed a low CSF glucose.

In this study, it shows that mean CSF protein (mg/dl) in viral encephalitis was 52.59, bacterial meningitis was 57.92 & in severe malaria was 35.All patient with bacterial meningitis 13(100%) & most patients with viral meningo-encephalitis 15(88.2%) revealed raised CSF protein.

In this study, it shows that mean CSF WBC (cell/mm3) in viral encephalitis was 22.59, bacterial meningitis was 676.92 & in severe malaria was 3.31. It also shows differential count of CSF WBC in different type of meningitis. In Bacterial meningitis it is neutrophils & in other type of meningitis it is the lymphocyte.

According to Simko et al, in encephalitis vs. meningitis; it showed CSF WBCs/mm3 202 (2-667) vs. 484 (58-1888), <10 CSF cells/mm3 19% vs. 12%, % of CSF Lymphocyte 76 (16-97) vs. 87 (43-100), CSF RBCs/mm3 2518 (0-27,566) vs. 54 (0-711) and CSF Protein(mg/dL) 73 (22-146) vs. 129 (75-281)15. According to Van DeBeek et al, predictors of bacterial etiology considering CSF glucose < 40, CSF protein > 60, CSF neutrophil count > 80%, CSF WBC count > 100, CSF: Serum glucose ratio < 0.23 showed that presence of any ONE of the above findings predicts bacterial etiology with > 75% certainty.[16]And considering CSF glucose < 34, CSF: Serum glucose ratio < 0.23, CSF protein > 220 mg/dl, CSF WBC count > 2000/mm3, CSF neutrophil count > 1180/mm3 showed presence of any ONE of the above findings predicts bacterial etiology with > 99% certainty[17].

Sometimes patients attendants fail to give adequate history. Patients were taking prior antibiotics which may alter the CSF findings. The study was carried out in low resource situation And the study may not represent the overall situation of Bangladesh, as only 50 cases were observed and the study was carried out in a particular period of time and in malaria endemic zone of Bangladesh.

Patient presents with acute fever and altered mental state with or without neurologic deficit & new onset seizure, particularly if there is signs of meningeal's irritation patient should be screened for acute meningo-encephalitis syndrome.

In our country laboratory facilities are very limited.PCR for virus and AFB is not always permissible due to poor economic status of patient. Even CSF culture and other serologic test are not readily available in most of the district town. So proper history taking & accurate clinical examination and minimum laboratory investigation to screen acute meningo-encephalitis syndrome like CSF study for biochemistry, cytology & Gram stain and blood film for malarial parasite in malaria prone zone. And sometime brain imaging and metabolic profile is recommended in selective cases if clinical data suggest.

Though fundoscopy was not included as differentiating parameter but during this study, it was observed that fundoscopy might be a good clinical tools to identify malarial retinopathy and to detect risk factors of stroke like hypertensive & diabetic retinopathy and to exclude mass effect or papillodema. Extra-neurologic sign like meningococcal skin rash, black water fever, and jaundice in severe malaria may also be used as differentiating parameter.

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CASE REPORT

A Patient with Sub Acute Viral Hepatitis (HEV) and Nonalcoholic Wernicke's Encephalopathy: A Case Report

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Abstract:

Wernicke's encephalopathy (WE) is an acute neurological disorder resulting from thiamine deficiency. It is mainly related to alcohol abuse but it can be associated with other conditions such as gastrointestinal disorders like hyperemesis. A 38-year-old man with acute viral hepatitis presented with severe weakness, yellow discoloration of the body, hyperemesis in addition with disorientation, horizontal and vertical gaze-evoked nystagmus. MRI of brain showed typical findings of WE. Adequate treatment with parenteral thiamine was given. Neurological symptoms (Disorientation, Nystagmus and Ataxia) ameliorated during hospital stay and radiological abnormalities markedly improved in a follow up MRI after 2 months. This case suggests that WE may be associated with hyperemesis in non-alcoholic patients. Early thiamine treatment in symptomatic patients may improve prognosis. This extraordinary presentation of WE with hyperemesis, encouraged us to presentthis case history.

Keywords: *Hyperemesis, Thiamine, Wernicke's encephalopathy (WE)etc.*

Introduction:

Glucose which is the main source of energy for many tissue especially brain which is metabolized by glycolysis pathway to produce pyruvate. Pyruvate is further degrading into acetyl Co-A which further utilized in citric acid cycle pathway thereby producing ATPs (Flow chart).Thiamine, or vitamin B1, plays an essential role in glucose metabolism & nerve cell function. Thiamine pyrophosphate (TPP) constitutes the active form of thiamine. TPP, as a coenzyme, is a necessary part of complexes such as the dehydrogenase complex and the alpha-ketoglutarate dehydrogenase complex. These enzyme complexes are key rate-limiting enzymes, involved in the metabolism of glucose. Thus thiamine deficiency can cause metabolic disturbance of glucose in vulnerable brain regions.Thiamine is found in beef, liver, dried milk, nuts, oats, oranges, pork, eggs, seeds, legumes, peas and yeast. Daily need of thiamin in adult is 1.2 mg per day. Malnutrition (due to alcohol abuse, unbalanced diet, hyperemesis, starvation, renal dialysis, cancer, AIDS, or even gastric surgery) is the main cause of thiamin deficiency. Thiamin deficiency results in diffuse polyneuropathy, high-output heart failure, and Wernicke-Korsakoff syndrome[1].

Wernicke's encephalopathy (WE) or Wernicke's disease is an acute and treatable neurological disorder due to deficiency of thiamine (vitamin B1)[2]. In Bangladesh malnutrition (due to unbalanced diet, hyperemesis, starvation, renal dialysis, cancer, AIDS, or even gastric surgery) is the main risk, though alcohol abuse is the main cause in world wide. The characteristic clinical triad is that of Ophthalmoplegia, Ataxia, and Confusion[1]. However, only one third of patients present with all three features[6]. Most patients are profoundly disoriented, indifferent, and inattentive, although rarely they have an agitated delirium related to

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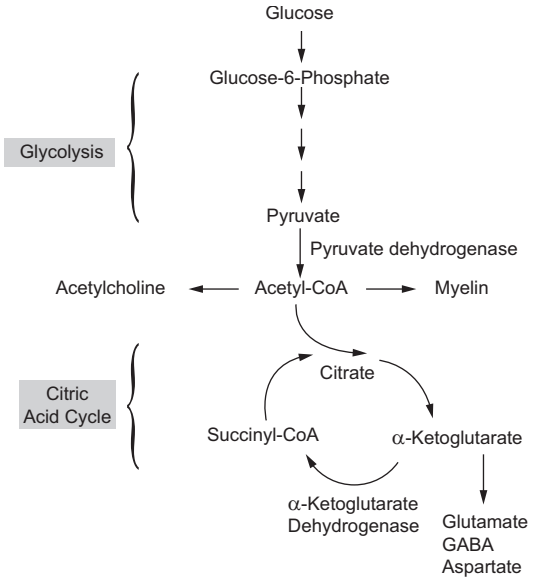
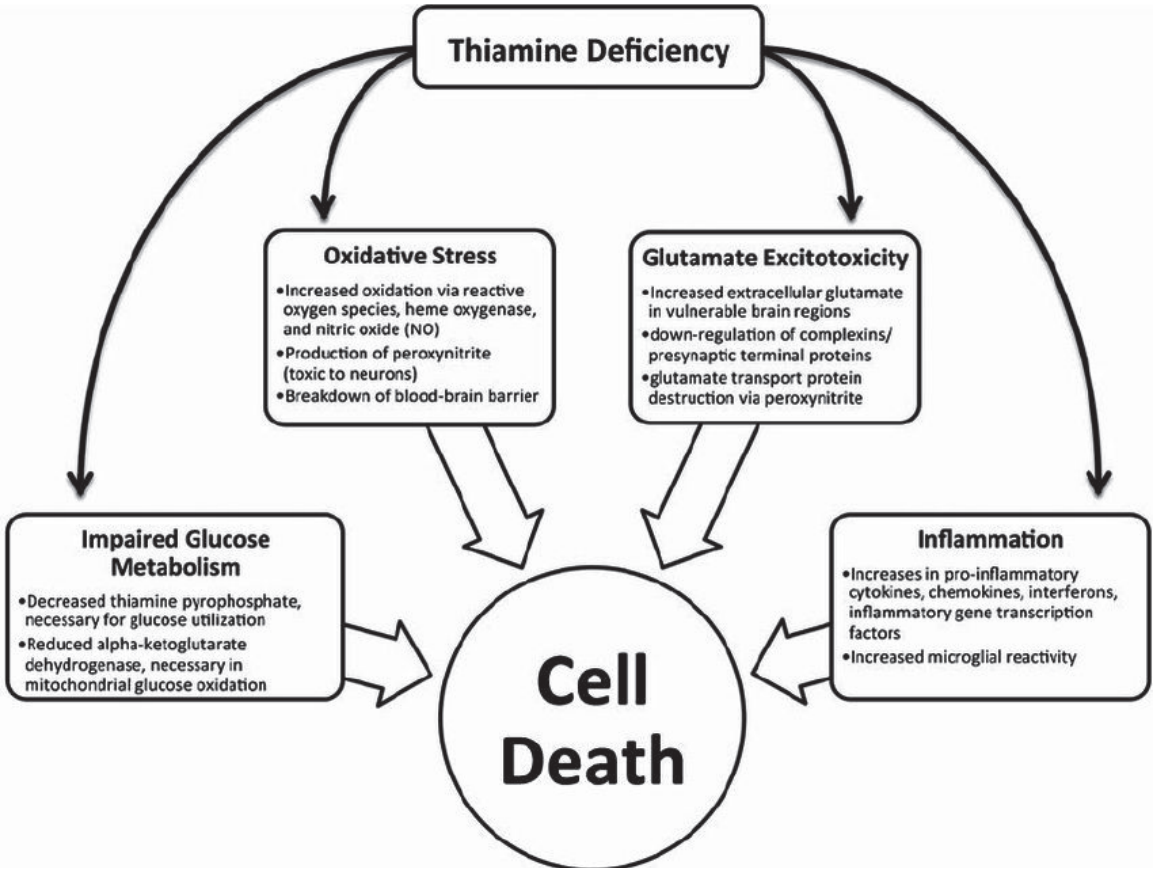
ethanol withdrawal. If the disease is not treated, stupor, coma, and death may ensue. Symptomatic thiamine deficiency in non-alcoholic patients is a less recognized and often misdiagnosed condition. The diagnosis of WE is mostly made clinically; nevertheless, magnetic resonance imaging (MRI) has been recognized as a useful adjunct in diagnosis.

WE is treatable disease with thiamine supplementation, which can lead to improvement of the symptoms and often complete resolution, particularly in those where alcohol abuse is not the underlying cause. Often other nutrients also need to be replaced, depending on the cause.

However, there are few reports of WE with Hyperemesis in nonalcoholic patients. In the present case, suggesting that he may have experienced thiamine deficiency caused by anorexia and severe vomiting.



Flowchart: Glucose metabolism



Flow chart: Pathogenesis of WE

Case report:

A previously healthy 38-year-old man was admitted to BSMMU with irrelevant talking, ataxia, drowsy& restless of last 15 days. Before admission, the patient suffering from severe anorexia, vomiting & yellow discoloration of skin for two and half - months. The patient's personal history revealed that he did not have a habit of alcohol abuse. Physical examination revealed he is disoriented, anemic, icteric, pulse 82/min, blood pressure 110/70 mmHg, and tender hepatomegaly but there was no thyroid enlargement or palpable lymph nodes. Ocular movement examination revealed horizontal and vertical gaze-evoked nystagmus. In addition, the patient exhibited diplopia, deep tendon reflexes were diminished and severe muscle weakness and positive Babinski's sign on both side. Sensory examination couldn't evaluated due to disorientation and restlessness

He had elevated level of Bilirubin 11.2 mg/dl (normal limit ; 0.2-1.2mg/dl) , Random plasma glucose 4.7 mmol/L (reference value : <7.8 mmol/L) plasma AST 76 U/L (SGOT; normal limit: < 50 U/L) , plasma ALT 1904 U/L (SGPT; normal limit: <50 U/L), Serum Amylase 75.58 U/L (normal limit : 25-115 U/L) , Prothrombin time; patient's: 18.10sec (reference value 12 16 seconds) with INR 1.51 , Serum total protein 77 gm/L (reference value : 64 –83 gm/L), Serum Albumin 40gm/L (reference value : 37.95 – 53.99 g/L) , Gamma-GT 36.3 U/L (reference value : < 55 U/L) , Alkaline Phosphatase 495 U/L (reference value : 30 - 120 U/L) , Serum CA 19-9 5.1 U/ml (reference value : < 37 U/ml) Hemoglobin 12.4 g/dl (normal range : 15±2 gm/dl) , ESR 90 mm/ 1st hour (normal range : 0 – 10 mm/ 1st hour) , total WBC count 6000/cmm , platelet count 310000/cmm ,Serum electrolytes; Sodium 135 mmol/l , Potassium 4.8 mmol/l , Chloride 95 mmol/ l , Serum Creatinine 0.71mg/dl (reference value : 0.6 – 1.4 mg/dl) Anti HEV IgM positive , Anti HBs & Anti HBc (total) also positive , USG of whole abdomen revealed hepatomegaly with darker liver & coarse bright hepatic parenchyma , ESR 90mm/ 1st hour , Erosive gastritis on endoscopy.

Because of his inability to swallow, the patient initially received nutritional support by intravenous infusion and after a few days a nasogastric feeding tube was placed for maintain nutrition and medication. Initially he was diagnosed as a case of subacute viral hepatitis due to HEV and the investigations concentrated to exclude chronic liver disease. Upper GIT endoscopy revealed erosive gastritis & USG of whole abdomen revealed hepatomegaly with darker liver & coarse bright hepatic parenchyma. Then the patient was examined by a neurologist and ocular movement examination revealed horizontal and vertical gaze-evoked nystagmus. In addition, the patient exhibited diplopia, absence of deep tendon reflexes and positive Babinski's sign and suspected that the patient was suffering from Wernicke's encephalopathy. Serum thiamine couldn't be measured due to unavailability but MRI of brain showed bilateral symmetrical T2WI and FLAIR hyper intense signal changes were noted in the peri-aqueductal region, dorsal brain stem, medial thalami surrounding the 3rd ventricle, post contrast showed mild enhancement of the lesion (Figure-1). Therefore, immediate treatment was given. Patient received intravenous thiamine

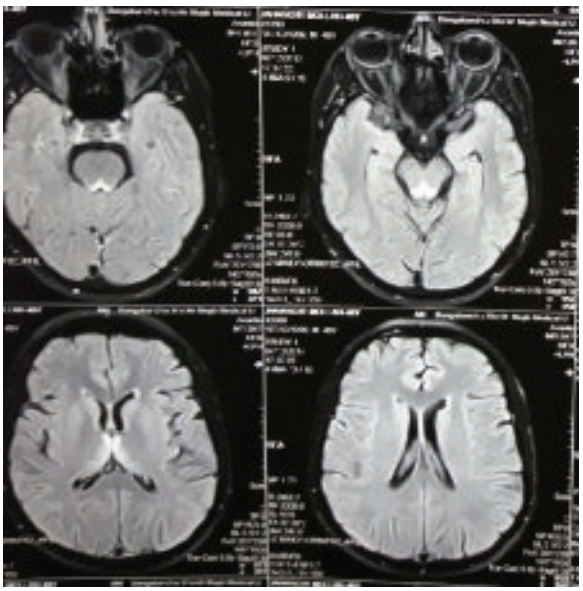


Fig.-1: *Axial FLAIR images showing the periaqueductal gray (a, b), bilateral thalamus (c), the front lateral ventricle (d) These areas typically show hyper intensities in Wernicke encephalopathy*

200mg per dose 8 hourly. After 3 days neurological symptoms and sign improved including ataxia and nystagmus. Total 7days intravenous thiamine was given. After 7 days he was discharged with the advice of oral thiamine 300mg daily in divided doses for 2 months. Review MRI of brain was done after 2 months and revealed disappearing previous hyper intense signal changes in the previously mentioned areas (Figure – 2).

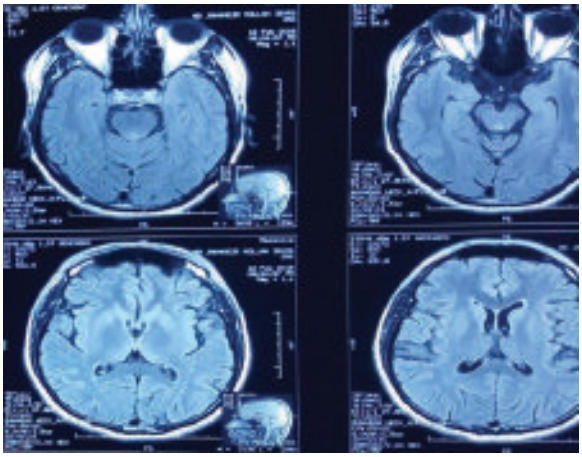


Fig.-2: *Two months after treatment, axial FLAIR images demonstrated a more obvious improvement in the periaqueductal gray (a, b) and thalamus (c,) the front lateral ventricle (d).*

Discussion:

WE is a relatively common neurological condition, typically caused by short-term deficiency of thiamine in alcoholics[2]. WE can also arise from other causes, such as the hyperemesis, Crohn's disease, anorexia nervosa, fasting, starvation, malnutrition, AIDS, surgical treatment of gastrointestinal diseases and unbalanced diets[2-6]. WE is associated with several common clinical manifestations including eye signs, cerebellar signs, amnesia and altered mental state, seizures, frontal lobe dysfunction gastrointestinal symptoms. Classical triad WE are mental confusion, ataxia and ophthalmoparesis which is more frequent in alcoholics than non-alcoholics. In the present case, the patient did not exhibit alcoholism[7].

Understanding the precise pathogenesis of WE could be valuable for improving the accuracy of diagnosis and provision of appropriate treatments for the condition. Thiamine, or vitamin B1, plays an essential role in the functions of growth and development in normal cells. Thiamine pyrophosphate (TPP) constitutes the active form of thiamine. TPP, as a coenzyme, is a necessary part of complexes such as the dehydrogenase complex and the alpha-ketoglutarate dehydrogenase complex. These enzyme complexes are also key rate-limiting enzymes, involved in the metabolism of lipids, glucose and amino acids. Thus thiamine deficiency can cause metabolic disturbance in vulnerable brain regions[8-9].

Diagnosis of WE is usually dependent on clinical symptoms, changes in medical imaging results, and the measurement of thiamine[7]. EFNS guidelines recommend that at least two of the following four signs are present in the clinical diagnosis of WE in non-alcoholics: dietary deficiencies, eye signs, cerebellar dysfunction, and either an altered mental state or mild memory impairment[7].

The present case is a patient of acute viral hepatitis caused by Hepatitis E virus, who has intractable vomiting, severe anorexia, deep jaundice for which he was on parenteral nutrition for two months. Patient suddenly developed altered level of consciousness, imbalance & involuntary eye movements. Examinations showed patient is confused, disoriented, having gaze evoked nystagmus, bilateral lateral rectus palsy, cerebellar ataxia. These symptoms were one part of the diagnostic basis for WE.

Damage caused by metabolic disturbance from thiamine deficiency can result in oxidative stress, excitotoxicity of neurons, inflammatory responses, decreased neurogenesis, destruction of the blood–brain barrier, lactic acidosis and weakening astrocyte function In addition, selective damage to the medial and intralaminar nuclei of the thalamus, mammillary bodies, inferior colliculus, lateral vestibular nucleus, cerebellar vermis and other vulnerable areas has been observed where thiamine is processed and high levels of oxygen are consumed.

Taken together, damage to these areas is likely to lead to the related symptoms of WE. Therefore, radiographic imaging of these vulnerable areas may be valuable for diagnosing and treating WE patients. MRI can aid diagnosis of WE and can also be used in follow-up examinations to monitor prognosis. Generally, typical lesions are located in the thalamus, periaqueductal area and the mammillary body. In the present case, high intensity signals were observed in periaqueductal region, dorsal midbrain, and medial thalami surrounding the 3rd ventricle in T2 &FLAIR imaging. The lesions observed on T2 & FLAIR images were consistent with the vulnerable regions described above & clinical symptoms. The measurement of serum thiamine is useful in the diagnosis of patients with WE, but its limitations should be acknowledged. In the present case, the patient's level of serum thiamine was not measured.

The presented patient was diagnosed as acute viral hepatitis due to HEV infection evident by high serum bilirubin (11.2 mg/dl), high level of SGPT (1904 U/L), S.ALP (495 U/L) & positive IgM HEV antibody. Serum ammonia level was normal which excludes hepatic encephalopathy but EEG was not done in our patient.

As discussed above, our patient experienced severe vomiting, anorexia, received parenteral nutrition for two months and exhibited classical symptoms, encephalopathy, ataxia, ophthalmoparesis (Bilateral abducence palsy) and nystagmus. In addition, there were obvious changes in radiological imaging results. Despite the patient's serum thiamine levels unmeasured, a primary diagnosis of WE arising from nutritional deficiency due to severe vomiting, anorexia can be made from these data.

Diagnosis of WE constitutes a medical emergency. When patients do not exhibit alcohol abuse, neurological damage may be serious and acute. Therefore, immediate treatment is important.

The patient in our case was given intravenous thiamine 200 mg three times/day for 7 days then oral thiamine 100mg three times daily was prescribed for next 2 months. The patient's symptoms were rapidly improved within 1 week, and the number of lesions was markedly decreased in follow-up FLAIR imaging.

Conclusions:

Wernicke's encephalopathy is probably an underdiagnosed condition, mainly in nonalcoholic patients. Thiamine deficiency can pass unnoticed clinically, while an established deficiency can manifest in the form of neurological symptoms other than those classically described in WE. We need to identify patients at risk due to dietary restriction or malabsorption of vitamins, since the early establishment of thiamine treatment rapidly improves acute symptoms and long-term prognosis. Prophylactic administration of vitamin supplements in such risk groups should be considered as a routine clinical practice

Declaration of conflicting interests:

The authors declare no conûicts of interest in preparing this article.

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A Case of Adulthood Joubert Syndrome

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Abstract:

Joubert Syndrome is a rare autosomal recessive disorder characterized by hypotonia, ataxia, breathing difficulties, developmental delay with hallmark molar tooth appearance in MRI. We report a rare case of adulthood Joubert Syndrome which is an unusual presentation. A 25 -years male presented to our outpatient department with developmental delay, dysphasia, ataxia, nystagmus, bilateral optic atrophy and hyperreflexia. MRI Brain showed classical 'molar tooth' appearance of cerebellar peduncles. Although an uncommon disorder, it is important to diagnose the condition early as physiotherapy and rehabilitation can be effective in coping with the symptoms causing developmental delay.

Key words: *Joubert Syndrome, Hypotonia, Ataxia, Pigmentary Retinopathy, Developmental Delay etc.*

Introduction:

Joubert syndrome (JS) was first described as a familial syndrome in 1969 by Marie Joubert in four siblings having agenesis of the cerebellar vermis presenting with episodic hyperpnoea, abnormal eye movements, ataxia and intellectual disability[1]. Several years later, midbrain-hindbrain malformation, the"molar tooth sign" (MTS), was detected first in JS and was considered as pathognomonic sign[2].The term "Joubert Syndrome and Related Disorders" (JSRD) was then introduced to describe all conditions sharing the MTS[3], and this neuro-radiological sign is now considered as the mandatory criterion to diagnose JSRD. Many patients die in infancy or childhood due to marked breathing problems, but some survive into adulthood with variable cognitive and motor impairments[4,5] . Here, we discuss an adult case which was diagnosed principally by magnetic resonance imaging (MRI) finding of the typical "molar tooth sign", and by manifestation of other related clinical symptoms, including mental retardation, dysphasia, nystagmus and longstanding ataxia. To the best of our knowledge, this is the first report on an adult JS male individual in Bangladesh.

Case Report:

A 25 years old male attended our outpatient department with parental complaints on his difficulties in speech, walk and vision. According to his mother's statement, her child was floppy after birth, suggesting hypotonia. He also had history of frequent hospitalizations due to breathing difficulties in first few months of his life. As no documents are available, we can only assume that patient might have suffered from alternate apnea & hyperpnoea. Patient had delayed milestones of development & cannot speak at all. He also had progressive loss of his vision. Patient has five siblings, all are in good health and there is no significant family history including consanguinity. Patient did not receive any formal education but he could perform his own personal care activities, such as independent bathing, dressing and toileting. Physical examination showed deviation of head to right side, bilateral horizontal & rotatory nystagmus with failure to abduct both eyes on

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lateral gaze (Figure 1,2). Patient doesn't interact properly and cannot speak at all. Visual acuity & intelligence could not be assessed properly. Fundoscopy revealed bilateral optic atrophy with tessellated fundus (Figure3). Tone was normal in upper limbs, but increased in the form of spasticity in both lower limbs. Muscle power was normal. There was generalized hyperreflexia with bilateral ill-sustained ankle clonus. Plantar response was extensor bilaterally on Oppenheim's maneuver. Bilateral intention tremor was present with past pointing. Gait was broad based & tandem gait was impaired. The patient, however, had no problems of breathing and other congenital anomalies. Axial MRI images obtained at the level of the midbrain showed a "molar tooth sign" typical in patients with JS (Figure 4). Further MRI image analysis revealed a bat wing-shaped fourth ventricle (Figure 5). Sagittal images additionally demonstrated hypoplasia of the vermis and dysgenesis of the corpus callosum (Figure 6). Putting all history, examination & MRI findings together the patient was diagnosed with JS. Ultrasound examination of the abdomen revealed normal appearance of the liver, spleen, and both kidneys. His complete blood count, renal function tests, liver function tests, blood glucose, and serum electrolytes all were within normal limit. We were not able to conduct any genetic analysis for the patient and his family due to the circumstantial limits. The patient was later treated with physiotherapy & other supportive management and his family was advised regarding general information on JS prognosis and patient support.

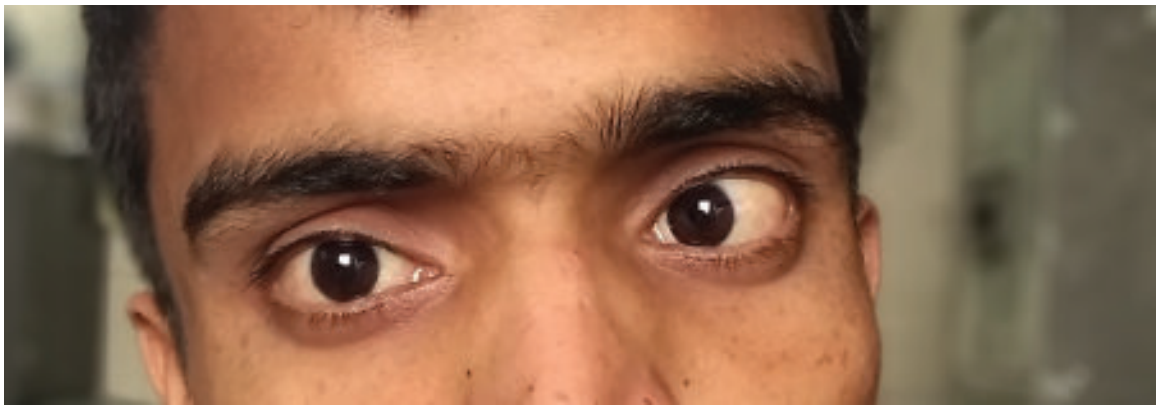

Fig.-1: *On right lateral gaze, patient has abduction failure of right eye. Patient also has head tilting toward right side*

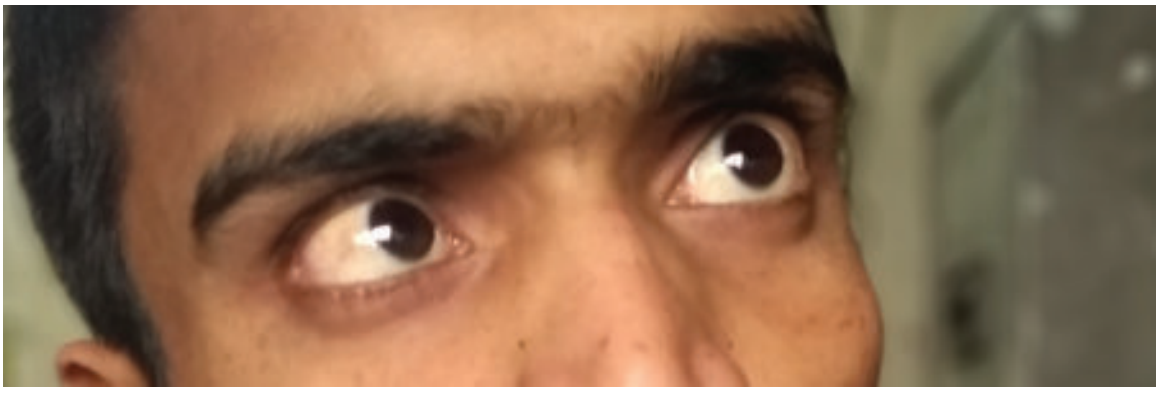

Fig.-2: *On left lateral gaze, patient has abduction failure of left eye with persistent head tilting toward right side.*

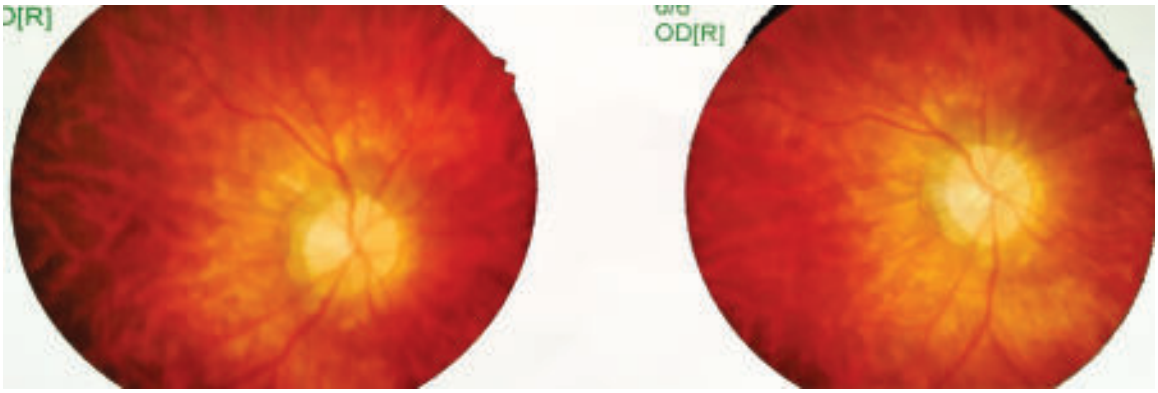

Fig.-3: *Fundal photography showing bilateral optic atrophy with tessellated fundus*

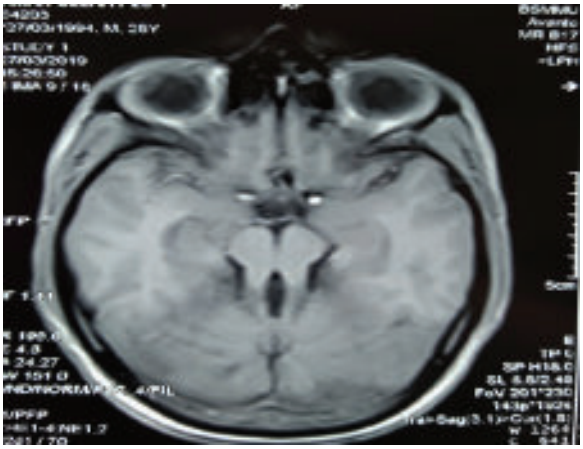

Fig.-4: *Axial T1WIMRI section showing "molar tooth" appearance of the midbrain due to elongation and horizontal orientation of the superior cerebellar peduncles and the small midbrain. Note increased depth and decreased width of inter-peduncular distance.*

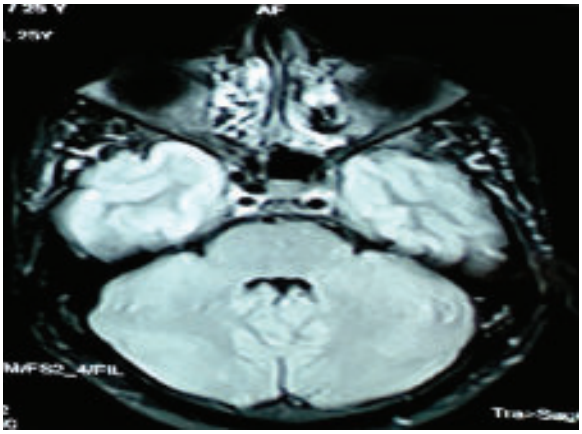

Fig.-5: *Axial FLAIR MRI sequence showing bat wing appearance of fourth ventricle*

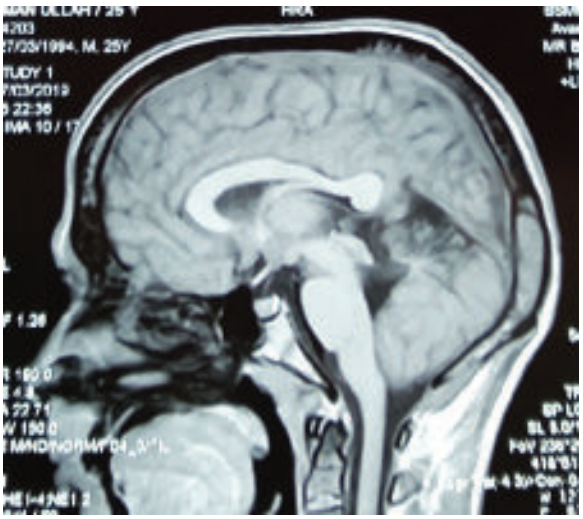

Fig.-6: *Sagittal T1WI MR image shows marked hypoplasia of the cerebellar vermis with corpus callosum dysgenesis*

Discussion:

JS is a rare autosomal recessive inherited disorder suspected by hypotonia, ataxia, developmental delay, intellectual disability with distinctive mid-hindbrain malformation (molar tooth sign), ocular abnormalities (e.g., pigmentary retinopathy, oculomotor apraxia, and nystagmus), renal cyst and hepatic fibrosis, hyperpnoea alternating with periods of apnoea[6]. Although the incidence of JSRD has not been precisely determined, it may range between 1/80,000 and 1/100,000 live births, but may be underestimated[7]. Though hypotonia at birth is a cardinal feature, in our patient we have found spasticity with generalized hyperreflexia, but

patient was floppy at birth suggesting hypotonia. We have also found other two cases with hyperreflexia, though tone was not increased[8,9]. Ocular manifestations are also variable & there is a reported case with bilateral papilloedema also[10].

The term "molar tooth" refers to the characteristic appearance of an enlarged and horizontally directed tubular structure on each side of the midline emerging from the midbrain. "The molar tooth sign" may be identified in 85%of patients with JS, and thus can be considered pathognomonic of this disorder[2].Inheritance of this disease is usually autosomal recessive, may be sporadic also. Studies have shown that it is a genetically heterogenous disorder with one locus pointing to chromosome 9q[11].In regions that lack genetic tests accessibility, neuroradiology should be used to assist final diagnosis[12].

Once a diagnosis of JSRD has been made, children should undergo further evaluations to assess the possible multiorgan involvement. Ocular investigations include assessment of visual acuity, ocular motility, fundus and, whenever possible, electro-retinogram. Slit lamp examination can reveal abnormalities of the anterior segment of the eye. Kidney and liver functions should be tested. Standard urine analysis is also necessary including urine specific gravity. Abdominal ultrasound is necessary to evaluate the kidneys (to detect small cysts and loss of cortico-medullary differentiation), and the liver (to identify hepatomegaly or underlying congenital hepatic fibrosis)[6].

Hence, there is no specific treatment for JS. Prognosis depends upon severity of symptoms and presence of associated anomalies but is generally poor due to the severe mental retardation in most cases. The main causes of death are severe feeding difficulties and respiratory infections with associated anomalies such as cranialmeningocele[13]. Respiratory abnormalities usually improve with increasing age of the patient, but cognitive and motor functions gradually decline[13]. Treatment for JS is therefore symptomatic and supportive. Multidisciplinary approach involving Infant stimulation, physical, occupational and speech therapy may have beneficial effects[14].

Diagnosis in adulthood is still valuable as diagnosing underlying possible multiorgan involvement can prevent significant morbidity & mortality.

Conclusion:

Today, it is still not possible to treat JS but it is possible to offer prenatal diagnosis and genetic counseling to those who have been diagnosed. Though commonly diagnosed in infancy & childhood, some patients may be undiagnosed till adulthood. Diagnosis of these patients is also important as prognosis in adult JS depends mostly on renal and hepatic complications that, if not timely diagnosed and managed, represent the major causes of death in JSRD patients.

List of abbreviations:

JS: Joubert syndrome; MTS: molar tooth sign; JSRD: Joubert syndrome and related disorders.

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