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## *ORIGINAL ARTICLES*

# Identification of Common Risk Factors Associated with Carpal Tunnel Syndrome

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**Abstract**

***Objective:*** *To identify the common risk factors associated with carpal tunnel syndrome.* ***Methodology:*** *This case-control observational study was conducted in the department of neurology and medicine, DMCH from May 2010 to April 2011 for a duration of 1 year. The study included purposively selected 80 persons. Patients attending the outdoor and admitted in indoor of department of neurology and medicine, DMCH with a clinically suspected CTS and established by electrophysiological parameters selected as cases (group –I) . Healthy volunteers and subjects who were devoid of any features of CTS but having history with isolated injury to the lower limb nerve and isolated facial nerve palsy with normal electrophysiological parameters selected as control (group –II). Data were collected by interview of the patients, clinical examination and laboratory investigations using the research instrument.* ***Result:*** *The mean age was 42.7±9.8 years with range from 24 to 64 years and 41.1±9.1 years with range from 26 to 61 years in group-I and group-II respectively. The proportion of male and female patients was similar in both the study groups. Male Female ratio was 1: 7 in both groups. In this study it was observed that hypothyroidism was found 25.0% in group I and 5.0% in group II, which was significantly ($p<0.05$) higher in carpal tunnel syndrome patients. Diabetes mellitus was significantly higher in carpal tunnel syndrome patients, which was 22.5% in group I and 7.5% in group II. Rheumatoid arthritis was found 20.0% in group I and 5.0% in group II, which was significantly ($p<0.05$) higher in patients with carpal tunnel syndrome. Pregnancy was found 11.4% in group I and 2.9% in group II. CKD with hemodialysis was found 17.5% and 7.5% in group I and group II respectively. In pregnancy and CKD with hemodialysis difference was not statistically significant ($p>0.05$) among the two groups. Regarding obesity it was found in this present series that 42.5% and 17.5% patients were obese in group I and group II respectively. Obesity was significantly ($p<0.05$) higher in patients with carpal tunnel syndrome. In this study it was found in multivariate analysis that patients with hypothyroidism 1.28 times, DM 2.20 times, RA disease 3.84 times, obesity 5.9 times more likely to be associated with carpal tunnel syndrome but CKD with hemodialysis patients and pregnancy were not significantly associated in multivariate analysis. In this study it was also found that almost a half (47.5%) of the patients was housewives followed by garment workers (27.5%) and clerical workers (22.5%) in group I, which indicates that carpal tunnel syndrome was more common among housewives.* ***Conclusion:*** *A conclusion can be*

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*made from the above mentioned result that CTS is multifactorial. Obesity, diabetes mellitus, hypothyroidism and rheumatoid arthritis are commonly associated with carpal tunnel syndrome. Moreover female sex and age were also associated with CTS. This study also found that patients diagnosed as having work-related CTS have a high prevalence of concurrent medical conditions capable of causing CTS without respect to any particular occupation.*

***Key Words:*** *Carpal tunnel syndrome, risk factors.*

**Introduction:**

Carpal tunnel syndrome (CTS) may be defined as the compression of the median nerve at the wrist (carpal tunnel) in the absence of an obvious injury, trauma or surgery. This is the commonest entrapment neuropathy[1-3]. The symptoms disturb sleep and affect performance at work. Many patients have to change their jobs or modify activities to decrease their symptoms[4,5].Women are three times more likely to develop CTS than men. The prevalence of CTS in general population has been estimated to be at 3-5.8% for women and 0.6-2.1% for men[6,7].

The associated conditions and disease for CTS are female sex, obesity, pregnancy and acromegaly, hypothyroidism, hemodialysis. rheumatoid arthritis and repeated use of vibrating hand tools, persons with diabetes or other metabolic disorders are also at high risk[8-13]. CTS usually affects only adult[1,14] .CTS have a relationship with diabetes mellitus, hypothyroidism and rheumatoid arthritis. For all three conditions, there are arguments that they are not simply concurrent with CTS but interact with the CTS development itself. Diabetes mellitus predisposes to development of peripheral neuropathy, which can make the median nerve more sensitive to alterations of the carpal tunnel and thus predisposes to CTS development. Hypothyroidism produces alterations of fluid balance and peripheral tissue oedema, which may lead to CTS development. The inflammatory process of rheumatoid arthritis can increase the pressure in the carpal tunnel, which may also lead to CTS[15].

Carpal tunnel syndrome cases have a significant correlation with higher BMI when compared to control subjects[16].BMI as an independent risk factor for CTS in both genders. Wrist index and hand anthropometrics were found to be independent risk factors for CTS in females but not in males[17]. Increase weight and more recently, body mass index as risk factor for CTS. Those individuals who were classified as obese (BMI>29) were 2.5 times more likely than slender individuals (BMI<20) to be diagnosed with CTS[18].So common risk factors are obesity, diabetes mellitus, hypothyroidism, rheumatoid arthritis and occupation[19-21].

Some cases of CTS are occupationally induced. The work related wrist and hand syndrome (repetitive motion injury) from cumulative trauma in the workplace have received increasing attention by the general public in recent years. Although a proportion of these cases have genuine CTS, longitudinal natural history data suggest that the majority of industrial workers do not develop symptoms of CTS[22]. Increased risk for the syndrome has been found in meat packers, garment workers, butchers, grocery checkers, electronic assembly workers, keyboard operators, musicians and housekeepers. The highest reported incidence of work-related CTS based on the number of carpal tunnel surgeries performed was 15% among a group of meat packers[23].

Neurophysiological investigation in the form of nerve conduction study (NCS) is a well established tool for the diagnosis and grading of CTS. The results of electro diagnostic studies have been found to be highly sensitive and specific[24-27]. Like other countries of the world, CTS is also assumed to be present in Bangladeshi population as all the precipitating factors are prevailing and in fact gradually increasing with the passage of time as females are increasingly being involved in various industrial works. On the other hand electrophysiological procedures including NCS have become quite available and popular in various centers of Bangladesh as a valuable investigation tool to diagnose entrapment neuropathies, like carpal tunnel syndrome. Like every where else,

neurophysiological investigation in the form of NCS is able to diagnose more than 84% of the clinically suspected CTS cases in Bangladeshi population[28]. It has been observed that there is no study regarding the risk factors associated with CTS in Bangladeshi population. Therefore a case-control syudy was done to identify the common risk factors associated with carpal tunnel syndrome.

**Methodology**

**Study design:**
Observational case controlled study.

**Place and period of Study:**
This study was carried out in the Department of Neurology and Medicine inpatient and outpatient department of Dhaka Medical College and Hospital (DMCH), Dhaka from May 2010 to April 2011 for duration of one year.

**Study population:**
Patients with a clinically suspected CTS and established by electrophysiological parameters.

**Sampling procedure:**
The required number of cases and controls were selected consecutively.

***Inclusion criteria:***

For cases (Group-I):

1) Clinical:
   a) Patients had typical clinical features of carpal tunnel syndrome. (Appendix-8.II)
   b) Patients who were willing to enter the study,
2) Electrophysiological (One or any combination of the following) :- ( Preston and Shapiro 1998).
   a) Median sensory distal latency more than 3.51 ms.
   b) Median motor distal latency more than 4.35 ms
   c) Median nerve CMAP less than 6.79 mv.
   d) Median nerve MNCV (motor nerve conduction velocity) less than 47.32 m/ sec.

**For controls :( Group-II)**

1) Clinical
   a) Healthy volunteers,
   b) Patients with isolated injury to the lower limb nerve or facial palsy
2) Electrophysiological- normal parameters (Preston and Shapiro .1998)
   a) Median sensory distal latency less than 3.51 ms
   b) Median motor distal latency less than 4.35 ms
   c) Median nerve CMAP more than 6.79 mv
   d) Median nerve MNCV more than 47.32 m/ sec

**Exclusion criteria for cases:**

- Symptoms less than 3 months,
- Conditions that mimics CTS such as cervical radiculopathy, proximal median neuropathy or significant polyneuropathy ,
- Cognitive impairment interfering with subjects ability to follow instructions and describe symptoms ,
- Patients who were above 70 years & below 18 years of age,
- Patients with carpal tunnel syndrome having history of hand trauma,
- Patient who refused to enter into the study.
- Patients with diabetes mellitus, nephrotic syndrome, myxoedema which might affect the blood lipid.
- Any other chronic clinical conditions which can alter lipid profile.
- Patients taking carbamazepine for less than two years.

**Data processing and statistical analysis:**
Analysis of data was done with the help of computer by SPSS programmed version of 16.0 software facilities. Appropriate statistical methods (unpaired t test, chi square test) were applied for data analysis and comparison. The significance of data was done

with 95% confidence interval taking p value d" 0.05 as significant.

**Results:**

The mean age was 42.7±9.8 years with range from 24 to 64 years and 41.1±9.1 years with range from 26 to 61 years in group-I and group-II respectively. The proportion of male and female patients was similar in both the study groups. Male Female ratio was 1: 7 in both groups.

The symptoms of the group-I subjects were tingling of the hands (60%) followed by pain (30%), numbness (25%), wasting (10%), and weakness (10%).The most of the control subjects were healthy volunteers (62.5%). Facial palsy constituted 12.5% and rest (25%) were isolated lower limb nerve injury. Regarding occupation almost a half (47.5%) of the patients was housewives followed by garment workers (27.5%) and clerical workers (22.5%) in group I. Regarding the affected hand it was found that right hand was more frequent, which was 55.0% and left hand was 10.0% in group I.

Hypothyroidism was found in 10(25.0%) cases in group I and 2(5.0%) in group II. The difference was statistically significant (p<0.05) between two groups regarding hypothyroidism.

Diabetes mellitus was found 9(22.5%) in group I and in 3(7.5%) cases in group II. The difference was not statistically significant (p>0.05) between two groups regarding diabetes mellitus.

Rheumatoid arthritis was found 8(20.0%) in group I and in 2(5.0%) cases in group II. The difference was statistically significant (p<0.05) between two groups regarding rheumatoid arthritis.

Pregnancy was found in 4(11.4%) cases in group I and in 1(2.9%) case in Group II. The difference was not statistically significant (p>0.05) between two groups regarding pregnancy.

Obesity was found in 17(42.5%) cases in group I and in 7(17.5%) cases in group II. The difference was statistically significant (p<0.05) between two groups regarding obesity.

CKD with hemodialysis was found in 7(17.5%) cases in group I and in 3(7.5%) cases in group II. The difference was not statistically significant (p>0.05) between two groups regarding CKD with hemodialysis.

In this study it was found in multivariate analysis that patients with hypothyroidism 1.28 times, DM 2.20 times, RA 3.84 times, obesity 5.9 times more likely to be associated with carpal tunnel syndrome but CKD with hemodialysis patients and pregnancy were not significantly associated in multivariate analysis.

**Table 1-A**

*Number of Hypothyroidism in group-I and group-II*

| | Group I (n=40) | | Group II (n=40) | | 95% CI | P value |
|---|---|---|---|---|---|---|
| Hypothyroidism | No. | % | No. | % | | |
| present | 10 | 25.0 | 2 | 5.0 | 6.33(1.16-45.51) | 0.012[s] |
| absent | 30 | 75.0 | 38 | 95.0 | | |

**Table 1-B**

*Number of diabetic mellitus in group-I and group -II*

| | Group I (n=40) | | Group II (n=40) | | 95% CI | P value |
|---|---|---|---|---|---|---|
| Diabetes mellitus | No. | % | No. | % | | |
| present | 9 | 22.5 | 3 | 7.5 | 3.58(0.79-18.46) | 0.060[ns] |
| absent | 31 | 77.5 | 37 | 92.5 | | |

**Table 1-C**

*Number of rheumatoid arthritis in group-I and group-II*

| | Group I(n=40) | | Group II(n=40) | | 95% CI | P value |
|---|---|---|---|---|---|---|
| Rheumatoid arthritis | No. | % | No. | % | | |
| present | 8 | 20.0 | 2 | 5.0 | 4.75(0.84-35.08) | 0.042[s] |
| absent | 32 | 80.0 | 38 | 95.0 | | |

**Table 1-D**

*Number of pregnancy in group-I and group-II.*

| | Group I(n=35) | | Group II(n=35) | | 95% CI | P value |
|---|---|---|---|---|---|---|
| Pregnancy | No. | % | No. | % | | |
| present | 4 | 11.4 | 1 | 2.9 | 4.39(0.42-108.9) | 0.176[ns] |
| absent | 31 | 88.6 | 34 | 97.1 | | |

**Table 1-E**

*Number of obesity in group-I and group-II.*

| | Group I(n=40) | | Group II(n=40) | | 95% CI | P value |
|---|---|---|---|---|---|---|
| Obesity | No. | % | No. | % | | |
| present | 17 | 42.5 | 7 | 17.5 | 3.48(1.12-11.13) | 0.014[s] |
| absent | 23 | 57.5 | 33 | 82.5 | | |

**Table 1-F**

*Number of CKD with hemodialysis in group-I and group-II.*

| | Group I(n=40) | | Group II(n=40) | | 95% CI | P value |
|---|---|---|---|---|---|---|
| CKD with hemodialysis | No. | % | No. | % | | |
| present | 7 | 17.5 | 3 | 7.5 | 2.62(0.54-14.07) | 0.176[ns] |
| absent | 33 | 82.5 | 37 | 92.5 | | |

**Table 2**

*Multivariate predictors of carpal tunnel syndrome with common risk factors (n=80)*

| | Crude | 95% CI | | P value | Adjusted | 95% CI | | P value |
|---|---|---|---|---|---|---|---|---|
| | OR | Lower | Upper | | OR | Lower | Upper | |
| Hypothyroidism | 6.33 | 1.16 | 45.51 | 0.012[s] | 1.28 | 0.91 | 11.81 | 0.047[s] |
| DM | 3.58 | 0.79 | 18.46 | 0.060[ns] | 2.20 | 1.28 | 21.06 | 0.021[s] |
| RA | 4.75 | 0.84 | 35.08 | 0.042[s] | 3.84 | 1.29 | 47.61 | 0.025[s] |
| Obesity | 3.48 | 1.12 | 11.13 | 0.014[s] | 5.90 | 1.54 | 22.61 | 0.010[s] |
| CKD withhemodialysis | 2.62 | 0.54 | 14.07 | 0.176[ns] | 1.12 | 0.23 | 5.44 | 0.880[ns] |
| Pregnancy | 4.39 | 0.42 | 108.9 | 0.176[ns] | 3.28 | 0.91 | 11.8 | 0.070[ns] |

**Discussion:**

This case controlled study was carried out with an aim to identify the common risk factors i.e. obesity, diabetes mellitus, hypothyroidism, rheumatoid arthritis associated with carpal tunnel syndrome in comparison with healthy persons. A total of 40 patients having symptoms of CTS and established by etectrophysiological parameters selected as cases and 40 subjects who were devoid of any feature of CTS and had normal etectrophysiological parameters with matching the background characteristics selected as control. This study was carried out in the Department of Neurology and Medicine, Dhaka Medical College Hospital (DMCH) during May, 2010 to April, 2011.

In this current study it was found that the mean (±SD) age was 42.7±9.8 years with range from 24 to 64 years and 41.1 ±9.1 years with range from 26 to 61 years in group I and group II respectively. The age distribution between two groups was almost similar, no significant ($p>0.05$) difference was found between two groups. Maximum number was found in the 5$^{th}$ decade in both groups. Similarly, Ferry et al. (2000) found the mean age was 41.9 years for both cases and controls[29]. In another study, Steven, John and Wing (1998) showed the mean age of their patients was 40 years and 83% aged between 25 to 54 years[30]. Vessey, Mackintosh and Yeates (1990) reported that standardized first referral rates for carpal tunnel syndrome doubled as age increased from 25-29 to 50 or more[31]. Ferry et al. (2000) and Zambelis, Tsivgoulis and Karandreas (2010) mentioned that the syndrome was associated in older age group, which is higher with the present study, this may be due to geographical and racial influences may have significant impacts on CTS[32].

In this present study male and female were found 12.5% and 87.5% respectively in both groups and male female ratio was 1:7, which indicates that carpal tunnel syndrome is more common in female. Solomon *et al*. (1999) found female 74.0%, which is consistent with the present study[12]. In another study Steven, John and Wing (1998) showed that 70.0 percent patients were female[30]. Ferry *et al*. (2000), Dieck and Kelsey (1985) and Zambelis, Tsivgoulis and Karameros (2010) mentioned that syndrome was associated in older age group of women with some hormonal factors, notably past use of oral contraceptives[29,32,33].

In this present series it was found that almost a half (47.5%) of the patients was housewives followed by garment workers (27.5%) and clerical workers (22.5%) in group I, which indicates that carpal tunnel syndrome was more common in housewives. Mattioli *et al* (2009) found that house wives were 3.8 fold higher than standardized rate[34]. The high rates for full-time housewives suggest that domestic chores should be investigated as a possible risk factor for CTS. A large proportion of patients (27.5%) were garment workers, hence ergonomic factors are likely to contribute in the causation of CTS. Steven, John and Wing (1998) hypothesized that many patients already medically certified with a diagnosis of work-related CTS in fact have an underlying medical condition that could cause these symptoms irrespective of occupation[30]. Peter *et al* (1992) study suggests that characteristics, not job-related factors, are the primary determinants of slowing of sensory conduction of the median nerve and carpal tunnel syndrome[35]. Regarding the affected hand it was found in this current series that both hands were affected, which was 55.0%, followed by right hand 35.0% and left hand 10.0% in group I.

In this study it was observed that hypothyroidism was found in 25.0% cases in group I and 5.0% in group II, which was significantly ($p<0.05$) higher in carpal tunnel syndrome patients OR=6.33 [95% CI (1.16-45.51)]. Solomon *et al.* (1999) showed hypothyroidism had significant risk factors OR=1.7; (95% CI 1.1, 2.8)[12]. Similarly, Steven, John and Wing (1998) mentioned that two metabolic diseases hypothyroidism and diabetes mellitus were most prevalent in their study patients[30].

In this series it was found that diabetic mellitus was significantly higher in carpal tunnel syndrome patients, which was 22.5% in group I and 7.5% in group II. In a study, Zambelis, Tsivgoulis and Karandreas (2010) showed that diabetes mellitus was more prevalent in patients with bilateral CTS[32]. Mota et al. (2001) mentioned that carpal tunnel syndrome occurred approximately in 50.0% of the diabetic patients, affecting their activity and decreasing the quality of their life[36]. Similarly,

Steven, John and Wing (1998), Solomon *et al.* (1999) and Ferry *et al.* (2000) reported that diabetes mellitus was the most prevalent, which are consistent with the current study[3,12,29,30].

In this current study it was found that rheumatoid arthritis was found in 20.0% cases in group I and in 5.0% cases in group II, which was significantly ($p<0.05$) higher in patients with carpal tunnel syndrome. Similarly, Ferry *et al*. (2000) and Solomon *et al.* (1999) mentioned that the cause of most CTS is not known, but numbers of diseases that affect the local architecture of the wrist are associated with it, including rheumatoid arthritis and Colles fracture[12,29].

In this present study it was found that pregnancy was found in 11.4% cases in group I and in 2.9% cases in group II. CKD with hemodialysis was found in 17.5% cases and in 7.5% cases in group I and group II respectively. In pregnancy and CKD with hemodialysis difference were not statistically significant ($p>0.05$). Solomon *et al.* (1999) reported that the pregnancy was not significantly associated with CTS, which support the present study[12].

Regarding the obesity it was found in this present series that 42.5% and 17.5% patients were obese in group I and group II respectively. Obesity was significantly ($p<0.05$) higher in patients with carpal tunnel syndrome. Vessey, Mackintosh and Yeates (1990) showed an increase in BMI of 1.99 to 2.6 causes doubling of carpal tunnel syndrome[31]. In another study, Peter *et al.* (1992) reported that weight and BMI were strongly and positively correlated with the maximum latency difference (MLD)[35]. The risk for abnormal nerve conduction averaged 3.5-fold and 4.1-fold greater, respectively in the obese workers than in the slender workers. Similarly, Zambelis, Tsivgoulis and Karandreas(2010) and Steven, John and Wing (1998) found higher BMI was more prevalent in patients with bilateral CTS[30,31].

In this study it was found in multivariate analysis that patients with hypothyroidism 1.28 times, DM 2.20 times, RA 3.84 times, obesity 5.9 times more likely to be associated with carpal tunnel syndrome but CKD with hemodialysis patients and pregnancy were not significantly associated in multivariate analysis. Karpitskaya, Novak and Mackinnon (2002) mentioned that Carpal tunnel syndrome (CTS) had been frequently associated with physical factors and personal factors including smoking, obesity, diabetes mellitus, and hypothyroidism[37]. There were more CTS patients than control subjects who were obese ($p=0.02$; OR=1.77), had diabetes ($p=0.03$; OR=3.02), and hypothyroidism ($p=0.02$; OR=3.70), which is comparable with the present study. In another study, Stevens *et al.* (1992) showed rheumatoid arthritis and diabetes mellitus were significantly more frequent among the study patients with carpal tunnel syndrome than in the general population. The standardized morbidity ratio was 3.6 for rheumatoid arthritis and 2.3 for diabetes mellitus. Similarly, Steven, John and Wing (1998) mentioned that many medical conditions, including diabetes mellitus, thyroid disease, wrist osteoarthritis, and any form of inflammation affecting the wrist joints or tendon sheaths are associated with CTS[30]. Solomon *et al*. (1999) developed a multivariate model and found inflammatory arthritis was strongly associated with carpal tunnel release OR=2.9; (95% CI 2.2, 3.8)[12]. Several variables remained significant risk factors including female gender OR=1.6; (95% CI 1.3, 2.0), inflammatory arthritis OR=3.1; (95% CI 2.2, 4.2), diabetes OR=1.4; (95% CI 1.2, 1.8), hypothyroidism OR=1.7; (95% CI 1.1, 2.8), corticosteroid use OR=1.6; (95% CI 1.2, 2.1) and hemodialysis OR=9.0; 95% CI 4.2, 19.6). Both definitions of inflammatory arthritis were significantly associated with CTS surgery in unadjusted and multivariate analyses, and other variable point estimates were not changed. These results support current study that CTS is multi factorial, with such factors as hypothyroidism, diabetes, RA and obesity to be more prevalent in this group of CTS patients.

**Conclusion:**

A conclusion can be made from the above mentioned result that CTS is multi factorial. Obesity, diabetes mellitus, hypothyroidism and rheumatoid arthritis are commonly associated with carpal tunnel syndrome. Moreover female sex and age were also associated with CTS. This study also confirmed the hypothesis that patients diagnosed as having work-

related CTS have a high prevalence of concurrent medical conditions capable of causing CTS irrespective of any particular occupation

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# Diagnostic Role of Adenosine Deaminase (ADA) among Tuberculous Meningitis Patients

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**Abstract:**

***Background:*** *In the developing countries where TB is endemic; an ideal test for tuberculous meningitis should be economic, minimally invasive, of high accuracy and quick to perform.In many countries, also in India, several studies were conducted to establish the ADA activity as a sensitive and specific test of tuberculous meningitis.So it is very much needed to evaluate the diagnostic role of CSF ADA in tuberculous meningitis in Bangladesh.* ***Aim:*** *This study aimed to find out CSF ADA as a sensitive and specific test for early diagnosis of tuberculous meningitis.* ***Methods:*** *This case control study was carried out in the Department of Neurology, SSMC and Mitford Hospital, Dhaka from June 2011 to July 2012, to evaluate ADA activity in CSF for diagnosis of tuberculous meninigitis.* ***Results:*** *In the present study, sixty meningitis patients were enrolled. Of which, 30(50%) were tuberculous meningitis (TBM) taken as cases and rest 30(50%) were non-tuberculous meningitis (NTBM) taken as control.The CSF ADA activity from TBM patients was compared with CSF ADA from non-TBM infectious meningitis patients. The mean CSF ADA activity was found to be significantly higher in CSF of TBM patients, 14.01 ± 12.4 (1.0–65.2), mean ± SD with range, than in the CSF from non-TBM infectious meningitis, 7.2 ± 8.2 (1.8–49.1) P = 0.01.A cut-off value of >7.6 U/L for the TBM patients was calculated from the mean ±SD of the non-TBM patients.The ADA sensitivity is 81.82%,specificity 65.31%,accuracy 68.33%, PPV 34.62%,NPV 94.12%, positive likelyhood ratio 2.3 and lastly negative likelyhood ratio 0.2 for infectious TBM when this cut-off value was used.ROC curve shows area under curve of .736 suggests a moderate accuracy of the test in detection of tuberculous meningitis.* ***Conclusion:*** *This study demonstrated that ADA activity in the CSF of TBM patients, using a cut off value 7.6 U/L, can be useful for the early differential diagnosis of TBM. This test can be performed in any pathology laboratory where more sophisticated methods are not available.*

## Introduction:

Tuberculosis is one of the leading causes of mortality and morbidity in developing countries. The WHO reports puts to the record that globally, approximately 16 million people are suffering from active TB with an estimated 8.5 million developing active TB each year, resulting in approximately 2 million deaths[1]. Tuberculous meningitis (TBM) is a

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common infectious disease of the central nervous system in developing countries. Early diagnosis and treatment with chemotherapy and active management of the complications are of great importance to prevent the irreversible neurologic sequele and death. Delay in diagnosis and so in the start of effective treatment results in poor prognosis and sequalae in up to 25% of cases[2]. A definitive diagnosis of tuberculous meningitis depends on identifying Mycobacterium tuberculosis in the cerebrospinal fluid (CSF) by direct staining or culture. However, the diagnostic yield of CSF smears and cultures has been very low[3], and mycobacterial culture may take up to 6 weeks to yield results. Therefore, the diagnosis of tuberculous meningitis depends on the clinical manifestations of subacute to chronic meningitis with lymphocytic CSF and low CSF glucose levels. However, other forms of meningitis may mimic tuberculous meningitis. Certain patients with tuberculous meningitis may have CSF findings resembling aseptic meningitis. Several tests for the rapid diagnosis of tuberculous meningitis have been developed; all are based on examination of the CSF. These tests are considered indirect tests (usually measuring a product of the host response to his infection, such as adenosine deaminase(ADA), the radioactive bromide partition test and antibodies to the mycobacterial antigen) and direct tests usually measuring a product of the infecting organism, such as 3-(2'-ketohexyl) indoline, detecting of tuberculostearic acid (a component of the cell wall of M. tuberculosis), mycobacterial antigens or fragments of mycobacterial DNA by polymerase chain reaction[4]. These methods except adenosine deaminase are too complicated or expensive for many laboratories. Adenosine deaminase (ADA) is an enzyme involved in purine catabolism. It is considered as an indicator of cell-mediated immunity and is found mainly in T lymphocytes[5]. TBM is the severe form of extrapulmonary tuberculosis occurring in 7.0-12.0% of TB patients in developing countries with high rate of mortality due to delay in diagnosis and proper treatment[6]. In the absence of an early diagnosis and treatment, tuberculous meningitis is characterized by high mortality (20-50%) and morbidity (20-30%)[7].

The cytological and biochemical analysis of cerebrospinal fluid is the cornerstone for diagnosis but there are diagnostic difficulties many a times in differentiating tuberculous meningitis from nontubeculous meningitis. A gold standard for diagnosis of TBM is an identification of Mycobacterium tuberculosis in cerebrospinal fluid (CSF) by direct smear and culture.

Adenosine deaminase (ADA) is an enzyme with principal biological activity in T lymphocytes. It is required for lymphocyte proliferation and differentiation. The enzyme activity is known to be elevated in certain infection where immunity is cell mediated like in CSF of TBM patients[8-10]. Various studies have been conducted demonstrating CSF ADA estimation as an enzymatic assay in diagnosis of Tuberculous meningitis and can differentiate TBM from normal subjects or other infectious meningitis.

**Materials and Methods:**

It is a case control study. Thirty cases of tuberculous meningitis and thirty non-tuberculous meningitis cases were studied. All eligible subjects as per inclusion and exclusion criteria coming to the Department of Neurology and Medicine, Sir Salimullah Medical College & Mitford Hospital,Dhaka Medical College Hospital and Bangabandhu Sheikh Mujib Medical University from July 2011 to June 2012 were included till desired sample size was reached. The laboratory works were performed in the department of microbiology & immunology, BSMMU and Sir Salimullah Medical College, Dhaka.Sampling method was purposive and all meningitis patients seeking treatment were enrolled in the study as per following inclusion and exclusion criteria. They were of either sex, and age range was from fifteen years and above. Diagnosis of tuberculous meningitis were based on presence of clear sign and symptoms of TBM or presence of AFB in CSF. ZN stainining and /or culture positivity for AFB or good response to antituberculous drugs.The meningitis patients who failed to fulfill the above criteria were considered as nontuberculous meningitis and were taken as controls.

CSF ADA was carried out in all the patients of both tuberculous and non-tuberculous meningitis as per exclusion and inclusion criteria. Three CSF sample were collected, first was for cytological test, biochemical and microbiological test and second for CSF ADA and third was for CSF AFB culture. Two milliliters of CSF was sent for ADA assay.

**Statical Analysis:**

Among the meningitis patients tuberculous group were considered as cases and non tuberculous

group were considered as control. CSF ADA levels were compared between cases & controls. Data were compiled and analyzed by using SPSS version 16.0. Cut off value of ADA level for the diagnosis of tuberculous meningitis was done by using receiver operating characteristic curve (ROC) in the same version of SPSS. Student t- test was used for test of significance, $p<0.05$ was considered as statistically significant.

**Results:**

**Table-I**

*Distribution of the respondents by age and sex*

| | Frequency | Percentage |
|---|---|---|
| Age in years | | |
| 15- 20 | 7 | 11.7 |
| 20 - 39 | 32 | 53.3 |
| 40 - 49 | 10 | 16.7 |
| >=50 | 11 | 18.3 |
| Sex | | |
| Male | 34 | 56.7 |
| Female | 26 | 43.3 |

Table-I shows the distribution of the study subjects by age and sex. Among the subjects 11.7 % were aged below 20 years, 53.3% were aged between 20 - 39 years, 16.7% were aged between 40 - 49 years and 18.3% were aged above 50 years. Regarding sex 56.7% were male and 43.3% were female.

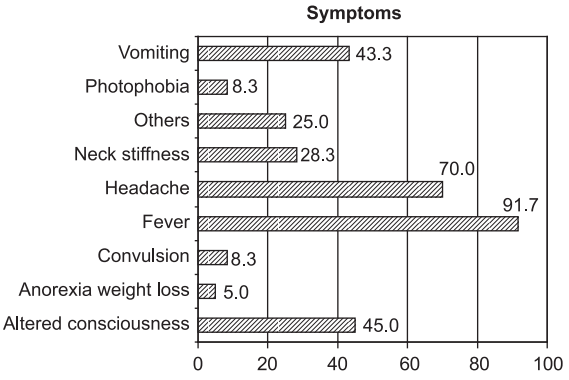


**Fig.-1:** *Distribution of the study subjects by presenting symptoms*

Figure-1 depicts the distribution of the study subjects by presenting symptoms. Among them most prevalent symptom was fever (91.7%). Among others, headache (70%), altered consciousness (45%), vomiting (43.3%) and neck stiffness (28.9%) were notable.

**Table-II**

*Distribution of the study subjects by physical sign*

| Physical sign | Frequency | Percentage |
|---|---|---|
| Neck Rigidity | 57 | 95.0 |
| Anemia | 33 | 55.0 |
| Kernig's sign | 28 | 46.7 |
| Long tract sign | 12 | 20.0 |
| Cranial Nerve Palsy | 6 | 10.0 |

Table II shows the distribution of the study subjects by physical sign. Among the study subjects 55.0% had anemia, 95.0% had neck rigidity, 10.0% had cranial nerve palsy, 46.7% had kernig's sign and 20.0% had long tract sign.

**Table-III**

*Distribution of the study subjects by fundoscopic examination findings*

| Findings | Frequency | Percentage |
|---|---|---|
| Normal | 50 | 83.3 |
| Papilloedema | 8 | 13.3 |
| Optic atrophy | 2 | 3.3 |
| Total | 60 | 100.0 |

Table III shows the distribution of the study subjects by fundoscopic examination findings, where 83.3 % had normal fundus, 13.3 % had papilloedema and 3.3 % had optic atrophy.

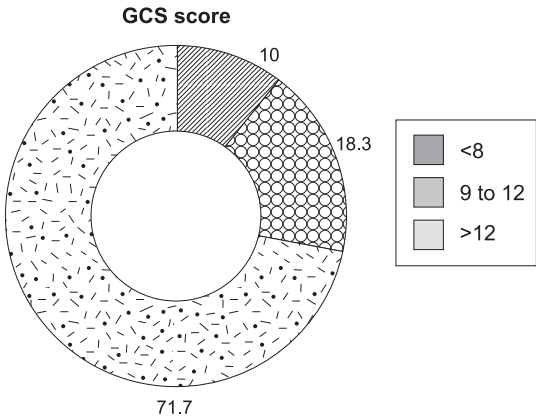


**Fig.-2:** *Distribution of the study subjects by GCS score*

Figure 2 shows the distribution of the study subjects by GCS score. Among the study subjects 10.0 % had GCS score less than 8, 18.3 % had between 9 – 12 and 71.7% had over > 12.

**Table -IV**

*Different parameters of CSF in **various** Meningitis*

| | Tuberculous(n=30) | | Bacterial(n=12) | | Viral(n=18) | |
|---|---|---|---|---|---|---|
| | Mean±SD | Range | Mean±SD | Range | Mean±SD | Range |
| Sugar (mmol/L) | 2.6 ± 1.2 | 0.8 – 6.5 | 2.606±1.2 | 0.4 – 4.5 | 4.01± 1.1 | 2.1 – 6.6 |
| Protein (mg/dl) | 212.3± 275.1 | 37 - 1440 | 142.1± 99.7 | 66 – 388 | 73.8 ± 55.2 | 21 - 226 |
| TC (/cmm) | 484.7± 1317 | 5 - 6400 | 192.4±199.9 | 5 – 840 | 27.24±48.3 | 0 - 180 |
| lymphocyte(%) | 72.08±31.2 | 10 - 100 | 31.25± 36.8 | 5 – 100 | 88.24± 23.4 | 10 - 100 |
| Polymorph(%) | 28.12±31.6 | 0 – 95 | 68.75±37.5 | 0 – 95 | 12.1±6.47 | 0 - 44 |

Table IV shows the different parameters of CSF in various meningitis. In TBM, sugar was low 2.6 ± 1.2 (range 0.8 – 6.5), protein was high 212.3± 275.(range 137 - 1440), total leucocytes count was high 484.7± 1317 (range 5 – 6400) and lymphocytic pleocytosis 72.08±31.2 (range 10 – 100). In bacterial meningitis, sugar was low 2.606±1.2 (range 0.4 – 4.5), protein was high 142.1± 99.7 (range 66 – 388),total cell count was high 192.4±199.9 (range 5 – 840) and polymorph was 68.75±37.5 (range 0 – 95).In viral meningitis,sugar was normal 4.01± 1.1 (range 2.1 – 6.6),protein was mildly high 73.8 ± 55.2 (range 21 - 226 ),cell count was high 27.24±48.3 (range 0 – 180) mostly lymphocytes 88.24± 23.4 (range 10 – 100).

**Table -V**

*Distribution of the Laboratory findings*

| | Frequency | Percentage |
|---|---|---|
| Gram Staining (n=60) | | |
| Positive cocci | 2 | 3.3 |
| Negative cocci | 58 | 96.7 |
| MT (n=30) | | |
| < 10 mm | 17 | 56.3 |
| > = 10 mm | 13 | 43.7 |

Table V shows the distribution of the laboratory finding. Among the study subjects 3.3% showed gram positive cocci in gram stain. And 43.7% showed MT over 10 mm. thirty subjects did not undergo MT as they were not the suspected TBM cases.

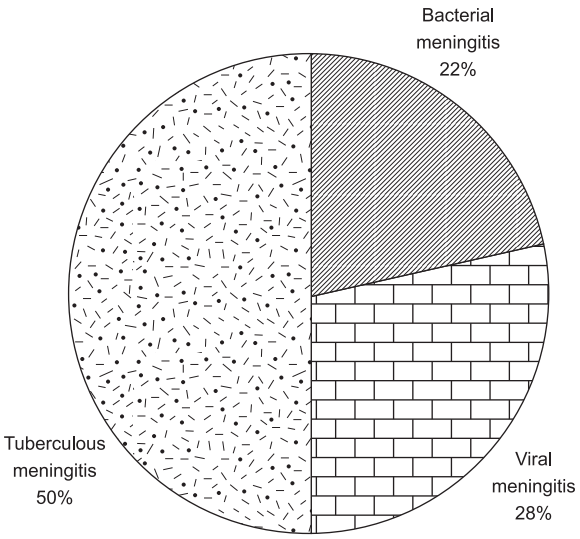


**Fig.-3:** *Distribution of the study subjects by diagnosis*

Sixty meningitis patients were enrolled in the study, of which, 50%(30) were tuberculous meningitis(TBM) and rest 50% (30) were nontuberculous meningitis(NTBM). Among the NTBM, 28% cases were viral meningitis and 22% cases were bacterial meningitis(Fig.3).

**Table -VI**

*CSF ADA level in comparision to CSF AFB culture and sensitivity (c/s) findings*

| CSF AFB C/S | CSF ADA(U/L) Mean±SD | Range(U/L) | P value |
|---|---|---|---|
| Positive(n=11) | 13.42±6.76 | 4.7-28.9 | 0.35 |
| Negative(n=49) | 9.97±11.69 | 1.0-65.2 | |

Table VI shows mean CSF ADA level. In AFB positive cases, it was 13.42±6.76 (range 4.7-28.9) and in AFB negative cases it was 9.9±11.69(range 1.0-65.2). ADA level was higher in AFB positve cases.

**Table-VII**

*CSF ADA result in various group of meningitis*

| Group | Mean ADA (U/L) | SD | Range of ADA (U/L) |
|---|---|---|---|
| TBM (n=30) | | | |
| Confirmed cases (11) | 13.4 | 6.76 | 4.7-28.9 |
| Probable cases (19) | 14.3 | 14.9 | 1.0-65.2 |
| Total (30) | 14.01 | 12.4 | 1.0-65.2 |
| Bacterial meningitis (n-12) | | | |
| Confirmed cases (n-2) | 6.2 | 1.1 | 5.4-7 |
| Probable cases (n-10) | 11.2 | 19.2 | 2.0-49.1 |
| Total (n-12) | 10.4 | 12.4 | 2.0-49.1 |
| Viral meningitis(n=18) | 5.09 | 1.92 | 1.8-8 |
| NTBM(n=30) | 7.2 | 8.2 | 1.8-49.1 |

In TBM ADA was positive in 20 cases and the mean was 18.3U/L (range 8.7-65.2U/l), ADA was negative in 10 cases and the mean was 5.34 U/L (range 1.0-7.0u/l). However, the overall result of ADA in TBM group was 14.01U/L±12.4, (range 1.0-65.2 U/L).In bacterial meningitis the ADA result was 10.4U/L±12.2, (range 2.0-49.1 U/L) and in viral meningitis 5.09U/L±1.92, (range 1.8-8 U/L).In NTBM ADA positve was in 6 cases and the mean was 15.9U/L (range 8-49.1), ADA negative was in 24 cases and the mean value was 4.6 (range 1.8-7.6 U/L) and the oveall result of ADA in NTBM group was 7.2U/L±8.2 (range 1.8-49.1 U/L). In TBM highest ADA was found 65.2 U/L and lowest was 1.0 U/L; in NTBM the highest ADA was 49.1 U/L and lowest ADA was 1.8 U/L.(Table VII).

**Table -VIII**

*Performance of CSF ADA activity*

| | AFB culture | | |
|---|---|---|---|
| ADA category | Positive | Negative | Total |
| ADA | 9 (81.8%) | 17(34.7%) | 26(43.3%) |
| > 7.6 U/L | (True Positive) | (False Positive) | (all ADA positive) |
| ADA | 2(18.2%) | 32(65.3%) | 34(56.7%) |
| < 7.6 U/L | (False Negative) | (True Negative) | (all ADA negative) |
| Total | 11(100%) (all CS positive) | 49(100%) (all CS Negative) | 60(100%) (Grand total) |

**Table -IX**

*Common tools of the performance of ADA activity:*

| Parameter | Result |
|---|---|
| Sensitivity(SEN) | 81.82% |
| Specificity(SPE) | 65.31% |
| Accuracy | 68.33% |
| Positive predictive value (PPV) | 34.62% |
| Negative predictive value (NPV) | 94.12% |
| Postive Likelihood ratio (LR+) | 2.3 |
| NegativeLikelihood ratio (LR-) | 0.2 |

Table X shows the performance of ADA activity to diagnose tuberculous meningitis. The true positive cases were 81.8%(9/11) and false negative were 18.2% (2/11); on the other hand the true negative cases were 65.3% (32/49) cases and false positive cases were 34.7%(17/49)). Total ADA positive was 43.3%(26/60) and total negative was 56.7%(34/60) among the 60 cases.

Table IX shows the various tools of performance of ADA activity: the ADA sensitivity was 81.82%,specificity 65.31%,accuracy 68.33%, PPV 34.62%,NPV 94.12%, positive likelihood ratio 2.3 and lastly negative liklihood ratio 0.2.

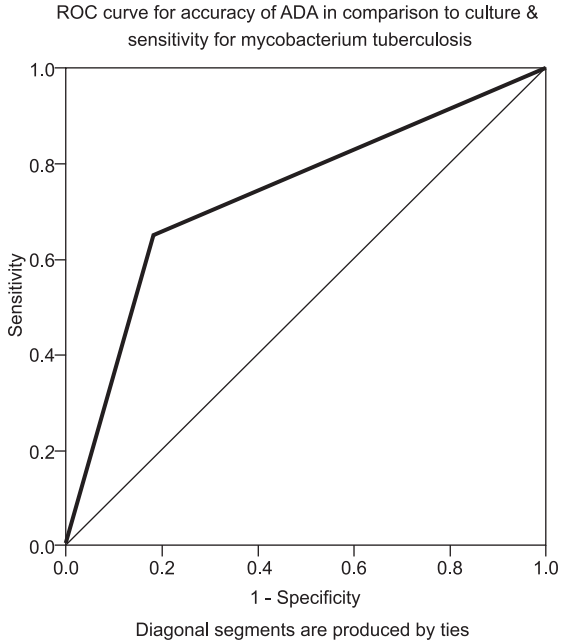


**Fig.-4:** *ROC curve for detecting accuracy of ADA in diagnosis of tuberculous meningitis*

ROC curve for accuracy of ADA in comparison to culture sensitivity for mycobacterium tuberculosis.

Area Under the Curve

| Area | Std. Error | P Value | 95% CI |
|---|---|---|---|
| .736 | .080 | .015 | 0.579 - 0.893 |

Test Result Variable(s): ADA category

Figure 4 shows ROC curve for detecting accuracy of ADA in diagnosis of tuberculous meningitis **;**Area under curve of .736 suggests a moderate accuracy of the test in detection of tubercular meningitis and Std. Error .080, P Value .015, 95% CI, 0.579 - 0.893.

**Discussion:**

The present study was done in 30 cases (TBM) and 30 control (NTBM).However,among the 30 TBM cases, one case was from NTBM group as intially diagnosed as pyogenic meningitis but latter on due to lack of antibiotic response and repeat CSF showed featues of TBM, it was included as TBM.Similarly two clinically suspected TBM cases were lastly diagnosed as meningitis due to lymphoma and another as Wilson's disease. So, these two cases were excluded from the study based on exclusion criteria. Sixty patients comprised 30 TBM, and 30 NTBM were selected that is similar to Rajendra *et al*[11] who took 56 cases comprised tuberculous meningitis:29, pyogenic meningitis : 15, and aseptic meningitis : 12 cases.The peak incidence in the present study was found in young adults in the age group of 20-39years (53.3%). It is similar to another study where observed the peak incidence was 43 %[12]. According to the present study, the incidence in male was 56.7% and in female 43.3%. The incidence in both males and females is consistent with the study done by Gambhir *et al.*[13]. The reasons for the high occurance of infection in male might be due to the fact that being the main earning member of the family; they have to go outside and thus are more exposed and more chances of getting infections. Moreover females are reluctant to come to the hospital for treatment.

In the present study, history of fever is present in most of the cases (91.7%). It was low-grade, more in the evening, associated with night sweats. In other study the incidence of fever was 87% and 58.9%[(14,15)] .Fever was absent in about 10% cases;litrature told that fever can be absent in upto 25% of patients[16]. Seizures of generalized tonic and clonic type were noted in 8.3% of the cases of both TBM and NTBM groups. In one study, the incidence of seizures was 12.1%[15]. The signs of meningeal irritation were present as neck rigidity in 95%, Kernig's sign in 46.7% .In another study, neck rigidity was 54% and Kernig's sign was 40% cases (Khatua *et al*., 1961) and on the other hand, neck rigidity was 100% in another study (Ramkrishna et al 2006).However in neurology text book, the overall meningeal signs is mentioned as 70%(Ashok,2008)

The present study revealed that cranial nerve palsies were observed in 10% (6/60)of the cases, which is consistent with the other study and that was observed in 15.4% (Venkataraman *et al*.,1980) cases. The commonnest was 6th 50%(3/6), then 7th 16.6%(1/6 case) and one was third cranial nerve palsy ;another one case was with multiple cranial nerve palsy (vi,vii,ix,x,xi,xii). In one study it was found 6$^{th}$nerve palsy in 7.2% cases[15] and also reported 3.2% cases with isolated facial nerve palsies[18]. In the present study, the incidence of papilloedema was 13.3 %( 8/60) and optic atrophy 3.3 %( 2/60) of cases and all are in TBM group. Other study observed papilloedema in 16.1% of cases[18]. In the present study, limb weakness was noted in 20%(12/60) cases, higher rate of observation was also found and the limb weakness was in 37.9% cases[18] but literaure review shows focal neurological findings was in 16-18%[19] that is more similar to present study. Similarly MT test shows higher rate of positivty in TBM patients and it was positive in 43.7%(13/30) cases.MT positive was found in 50% cases of TBM in another study[19].

The biochemical parameters of CSF in various meningitis showed some disimilarity between TBM and pyogenic meningitis for example CSF total cell count was higher in TBM than pyogenic meningitis.It was possibly due to getting partial treatment of pyogenic meningitis before coming to tertiary level hospital.Several case series have established CSF staining sensitivities of <20%[20,21]. However in the present study CSF ZN staning for AFB of all cases were negative.MTB culture studies in several case series established CSF culture sensitivities of 25 to 70%[22,23] and in one study shows the sensitivity of AFB culture is 40%[24]. In the present study 36.6%(11/30) cases were culture positive.Mean CSF ADA was higher in AFB positive cases than AFB negative cases, so there is a postive correlation between AFB and ADA.

In the interpretation of CSF-ADA levels for diagnosis of TBM two important points must be considered, one is the definition of TBM patients which may have a direct impact on the results of this interpretation and another is the value of cut-off which has a great importance in the evaluation of the sensitivity and specificity of the CSF-ADA test. The amount of this cut-off is controversial at the present time. Parsad *et al*[9] reported a sensitivity and specificity of 100% and 97.87% respectively with a 3.30IU/L cut-off value for ADA in the diagnosis of tuberculous meningitis. On the other hand, Chotmongkol *et al*[3] in their study reported 75% sensitivity and 93% specificity for CSF-ADA level in diagnosis of TBM with a 15.5I U/L cut off and Kashyap *et al.*[25] in their study reported that with a 11.39 IU/L cut-off, the sensitivity and specificity of ADA measurement in diagnosis of TBM in CSF samples of their patients were 82% and 83% respectively. Corral *et al*[26] reported 57% sensitivity and 87% specificity with a 8.5IU/L cut-off for CSF-ADA level in the diagnosis of TBM in HIV infected patients and Gambhir *et al*[13] in their study reported the sensitivity and specificity of 85% and 88.0% respectively for CSF-ADA levels in diagnosis of TBM with a 6.97IU/L cut off value. Baheti and his colleagues reported 95.85% sensitivity and 92.85% specificity for CSF-ADA test in differentiating tuberculous meningitis from non-tuberculous meningitis with a 6.5IU/L cut-off. Baro *et al.*[27] proposed a cut-off value of 6.5 U/L/min and showed sensitivity of 83.3% and specificity of 88.3%.

In this study, sensitivity and specificity of CSF-ADA level in comparison with MTB culture results in TBM diagnosis in 30 TBM patients with a 7.6 IU/L cut off were 81.82% and 65.31% respectively. Mean CSF ADA level was significantly higher in TBM patients (14.01±12.4) as compared to NTBM (7.2±8.2), P=0.01.

In the present study it was apparent that the level of CSF ADA activity in TBM was significantly high compared to overall NTBM group, but high level(>7.6U/l) was also observed in other individual group particularly bacterial meningitis (14.01U/l vs 10.4 U/l,TBM vs bacterial meningitis). The possible explanation is that the activity is usually higher in CSF which contains numerous cells. These findings are in agreement with other study where it was observed a high ADA activity in CSF obtained at the initial diagnostic lumbar puncture from bacterial meningitis cases[27]. It was also reported an overlap between TBM and non-TBM patients, especially for infectious neurological disorders like pyogenic meningitis[13]. It was also found that elevated levels

of CSF ADA are not specific for TBM. Diseases like pyogenic meningitis, CNS lymphoma, and fungal meningitis were shown to have elevated CSF ADA[27].

On the basis of present result when ADA interpreted together with clinical signs and symptoms and other laboratory tests, it can be a useful adjunctive rapid test for the diagnosis of TBM.The estimation of ADA activity in CSF is therefore serves as relatively simple, inexpensive and reliable tool in the diagnosis of TBM and management especially when other clinical laboratory tests are negative within sensitive limit.This study along with Gautam *et al*.and kashyap *et al* studies reemphasized that CSF-ADA level measurement can be used as a good, rapid and reliable laboratory test for diagnosing tuberculous meningitis at least in high prevalence and in cases of the incidence of tuberculosis in low income regions.

**Conclusion:**

The study found the sensitivity of the test to be 81.82%; specificity 65.31%, positive predictive value 34.62 % and negative predictive value 94.12%, and so it can be concluded that ADA estimation in CSF is not only simple, inexpensive and rapid but also fairly specific method for making a diagnosis of tuberculous etiology in TBM, especially when there is a dilemma of differentiating the tuberculous etiology from non-tuberculous. For this reason CSF ADA estimation in TBM may find a place as a routine investigation.

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# Association of Cytomegalovirus (CMV) Infection with Guillain-Barré Syndrome (GBS) In Tertiary Care Hospital (BSMMU) of Bangladesh

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**Abstract**:

***Background:*** *Guillain-Barré syndrome (GBS) usually preceded by infections, in particular cytomegalovirus (CMV). It may occur by primary infection, reinfection or by reactivation of CMV. Objective: The aim of the present study was to evaluate the association of Guillain-Barré syndrome (GBS) with Cytomegalovirus (CMV) infection.* ***Methodology:*** *This case control study was carried out in the indoor and outpatient Department of Neurology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from 1st January 2010 to 31st December 2011 for the duration of two years. All patients with GBS, who attended in neurology OPD or inpatient department at BSMMU during the study period, fulfilling the inclusion and exclusion criterias were included in this study. Age & sex matched volunteers, patients attendants, patients other than GBS who were non-diabetic, had no renal or hepatic diseases or family history of polyneuropathy were included in control group.* ***Results:*** *A total number of 78 respondents of which 39 patients were taken as cases and rest 39 were taken as controls who appeared in neurology OPD or inpatient department at BSMMU during the study period, fulfilling the inclusion and exclusion criterias were included in this study. The mean age ± SD of case and control groups were 30.82 ± 12.56 and 31.00 ± 12.77 years respectively (p=0.950). In case group the history of respiratory tract infection was present in 46.2% cases and absent in control group (p=0.001). In case group the history of gastroenteritis was present in 28.2% cases and absent in control group (p=0.001). In case group the history of fever was present in 30.8% cases and absent in control group (p=0.001). Anti-CMV IgM antibody was positive in 5.1% cases. Four fold rise of IgG in case group was present in 10.3% cases and absent in control group (p=0.040). Confirmed CMV infected GBS cases were 15.4% and absent in control group (p=0.011).* ***Conclusion:*** *The findings of this study permit to conclude that there is a significant association of Guillain-Barré syndrome (GBS) with Cytomegalovirus (CMV) infection.*

***Keywords:*** *Cytomegalovirus (CMV), Guillain-Barré Syndrome (GBS).*

## Introduction:

Guillain-Barré syndrome (GBS) now ranks as the most frequent cause of acute flaccid paralysis since the near-elimination of poliomyelitis throughout the world and its median annual incidence is 1 to 2 per 100,000 populations[1]. According to an epidemiologic survey, the average annual incidence of GBS in the United States is

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3.0 cases per 100,000 populations. With poliomyelitis under control in developed countries, GBS is the most important cause of acute flaccid paralysis.

GBS remains a diagnosis made primarily through the assessment of clinical history and findings[2].

In epidemiologic surveys, the overall death rate related to GBS ranges from 2-12% of patients. Deaths usually occur in ventilator-dependent patients, resulting from such complications as pneumonia, sepsis, adult respiratory distress syndrome, and less frequently, autonomic dysfunction[3]. Although the classic description of GBS is that of a demyelinating neuropathy with ascending weakness, many clinical variants have been well documented in the medical literature.

GBS is a post-infectious, immune-mediated disease. Cellular and humoral immune mechanisms probably play a role in its development. Most patients report an infectious illness in the weeks prior to the onset of GBS. Many of the identified infectious agents are thought to induce antibody production against specific gangliosides and glycolipids, such as $GM_1$, $GM_2$ and $GD_1$a etc, distributed throughout the myelin in the peripheral nervous system[4]. The favored hypothesis is that the immune response to certain infective agents in some people may trigger cross reactive immunity, with initially one or more myelin or axonal antigens leading to an autoimmune attack on the nerve tissue. Antiglycolipid antibodies have often been found in affected patients[5].

The pathophysiologic mechanism of an antecedent illness and of GBS can be typified by *Campylobacter jejuni infections*[6].

A preceding CMV infection with high titres of IgM antibody has been implicated in 10-15% of the patients with GBS[7].

Cytomegalovirus is a member of â herpes virus group. It is a DNA virus having double stranded DNA. It causes primary infection, reactivation or reinfection. Route of transmission are by breast milk, saliva, sexual transmission, blood transmission, organ transplantation and droplet infection etc[8].

In primary infection IgM against CMV develop and persist for 3-4 months, but in case of reinfection or reactivation IgM is not usually found, IgG is found. IgG is persist for life long[7]. It has also suggested raised concentrations of antibodies to ganglioside GM2 in patients with GBS after cytomegalo virus (CMV) infection[9]. The association between anti-ganglioside antibody responses and Guillan-Barré syndrome (GBS) after a recent cytomegalovirus (CMV) infection Khalili SA et al.[10], conducted a study. They concluded that antibodies to ganglioside GM2 are often associated with GBS after CMV infection, but their relevance is not known. It is unlikely that CMV infection and anti-ganglioside GM2 antibodies are solely responsible and an additional factor is required to elicit GBS[10].

Guillain-Barré syndrome may occur by primary infection or by reinfection or reactivation of CMV[11]. To study the association of cytomegalo virus infection with Guillian-Barre syndrome needs diagnosis of CMV infection which required at least one of the following laboratory method:- serology, specific intrathecal antibody production, virus isolation, direct detection of CMV PP65 antigen in blood, CMV culture, biopsy, positive specific immunohistochemical staining, polymerase chain reaction (PCR) assay etc[8].

Serological studies indicating an acute CMV infection includes:

1. The presence of positive IgM anti CMV antibodies with undectable CMV specific IgG antibodies, or
2. Presence of CMV specific IgG antibodies of low avidity in the presence or absence of virus specific IgM antibodies[11].
3. Presence of increase in the titre of IgG anti CMV antibodies in paired sample obtained during the infection[8].

This study was evaluated by serological test. The proposed study was evaluated the relationship of CMV infection with GBS. This study was focused on new insights into the epidemiology and information concerning the relationship between CMV infection and GBS.

**Methods:**

This is a case-control study. The study was carried out in the Department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. This study was conducted from 1st January 2010 to

31st December 2011 for the duration of two years. All patients with GBS, who attended in neurology department, BSMMU during the study period, fulfilling the inclusion and exclusion criteria were included in this study. Age & sex matched volunteers, patient's attendants who were non-diabetic, had no renal or hepatic diseases or family history polyneuropathy were included in control group. A total number of 78 study subject, 39 patients presented with Guillain-Barre syndrome and 39 controls were enrolled in this study by purposive sampling.

All data were compiled and edited meticulously by thorough checking and rechecking. All omissions and inconsistencies were corrected and were removed methodically.

All data were recorded systematically in preformed data collection form (questionnaire) and quantitative data was expressed as mean and standard deviation, and qualitative data was expressed as frequency distribution and percentage. Statistical analysis was performed by using Statistical Package for Social Science (SPSS) for windows version 12.0. 95% confidence limit was taken. Probability value <0.05 was considered as level of significance.

**Results and Observations:**

A total 78 number of study subjects 39 patients with GBS as cases and 39 volunteers, were taken as control who were attended in neurology department at BSMMU during the study period, fulfilling the inclusion and exclusion criteria were included in this study.

**Table-I**

*Distribution of the study subjects by IgG more than 4 fold rise (CMV positive) in the 2nd sample (n=78) . Sample – Blood*

| 4 fold rise of IgG | Group | | p value |
|---|---|---|---|
| | Case (n=39) | Control (n=39) | |
| Positive | 4 (10.3)# | 0 (0.0) | 0.124 |
| Negative | 35 (89.7) | 39(100.0) | |
| Total | 39(100) | 39(100) | |

*Chi-square test (after Yates correction) was done to measure the level of significance.

#Figure within parentheses indicates in percentage.

4 fold or more rise of IgG titre in 2nd sample considered as CMV positive.

Table I shows the distribution of the study subject by IgG more than 4 fold rise (CMV positive) in the 2nd sample. In the case group 4 (10.3%) cases showed 4 fold rise of IgG and the rest 35 (89.7%) cases showed negative results. In control group 4 fold rise of IgG was absent in all controls which was 39 (100.0%). The difference between case and control was not statistically significant (p=0.124).

In first case serum anti CMV IgG level in 1st sample was 85.1AU/ml and in 2nd sample was 854.1 AU/ml.

In second case serum anti CMV IgG level in 1st sample was 418AU/ml and in 2nd sample was 1219 AU/ml.

In third case serum anti CMV IgG level in 1st sample was 30.7AU/ml and in 2nd sample was 270AU/ml.

In forth case serum anti CMV IgG level in 1st sample was 36.1AU/ml and in 2nd sample was 320 AU/ml.

**Table-II**

*Distribution of the study subjects by Anti-CMV IgM (n=78). Sample – Blood*

| Anti CMV IgM | Group | | p value |
|---|---|---|---|
| | Case (n=39) | Control (n=39) | |
| Positive | 2(5.1) | 0(0.0) | 0.474 |
| Negative | 37(94.9) | 39(100.0) | |
| Total | 39(100.0) | 39(100.0) | |

*Chi-square test (after Yates correction) was done to measure the level of significance.

#Figure within parentheses indicates in percentage.

Serum anti CMV IgM positive considered as CMV positive.

Table II shows the distribution of the study subjects by anti CMV IgM. In case group anti CMV IgM was positive in 2 (5.1%) cases and the rest 37 (94.9%) cases were anti CMV IgM negative. In control group anti CMV IgM was negative in all 39 (100.0%) controls. The difference between case and control was not statistically significant (p=0.474).

**Table-III**

*Distribution of the Study subjects by CMV detection (n=78)*

| CMV detection | Group | | p value |
|---|---|---|---|
| | Case (n=39) | Control (n=39) | |
| Positive | 6(15.4)# | 0(0.0) | 0.034 |
| Negative | 33(84.6) | 39(100.0) | |
| Total | 39(100) | 39(100) | |

*Chi-square test (after Yates correction) was done to measure the level of significance.

#Figure within parentheses indicates in percentage.

CMV positive (by IgM = 02 and by 4 fold rise of IgG = 04)= 06.

Table III shows the distribution of the study subjects by CMV detection. In case group CMV was positive in 6 (15.4%) cases and the rest 33 (84.6%) cases were CMV negative. In control group CMV was negative in all 39 (100.0%) controls. The difference between case and control groups was statistically significant (p=0.034).

**Table-IV**

*Distribution of the study subjects by Anti-CMV IgG Sample-1 (n=78). Sample – Blood*

| Anti-CMV IgG (Sample-1) | Group | | p value |
|---|---|---|---|
| | Case (n=39) | Control (n=39) | |
| Positive | 33(84.6) | 37(94.9) | 0.135 |
| Negative | 6(15.4) | 2(5.1) | |
| Total | 39(100.0) | 39(100.0) | |

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

Figure within parentheses indicates in percentage.

Table IV shows the distribution of the study subjects by Anti-CMV IgG Sample-1. In case group Anti-CMV IgG (Sample-1) was positive in 33(84.6%) cases and negative in 6(15.4%) cases. In control group Anti-CMV IgG (Sample-1) was positive in 37(94.9%) controls and negative in 2(5.1%) controls. The difference between case and control was not statistically significant (p=0.135).

**Table-V**

*Distribution of the study subjects by Anti-CMV IgG Sample-2 (n=78). Sample – Blood*

| Anti-CMV IgG (Sample-2) | Group | | p value |
|---|---|---|---|
| | Case (n=39) | Control (n=39) | |
| Positive | 35(89.7) | 38(97.4) | 0.165 |
| Negative | 4(10.3) | 1(2.6) | |
| Total | 39(100.0) | 39(100.0) | |

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

Table V shows the distribution of the study subjects by Anti-CMV IgG Sample-2. In case group Anti-CMV IgG (Sample-2) was positive in 35(89.7%) cases and negative in 4(10.3%) cases. In control group Anti-CMV IgG (Sample-2) was positive in 38(97.4%) controls and negative in 1(2.6%) control. The difference between case and control was not statistically significant (p=0.165). Two sample of blood for serum anti CMV IgG antibody were taken to see the rising titre of IgG.

**Table-VI**

*Distribution of the study subjects by CMV, IgG (n=78). Sample – Blood*

| Anti-CMV, IgG by MEIA | Group | | p value |
|---|---|---|---|
| | Case (Mean ± SD) | Control (Mean ± SD) | |
| 1st Sample | 141.03 ± 268.80 | 61.99 ± 40.51 | 0.073 |
| 2nd Sample | 195.69 ± 266.12 | 61.22 ± 36.15 | 0.003 |

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

Table VI shows the distribution of the study subjects by CMV IgG. In case group the mean value of Anti-CMV, IgG by MEIA in 1st sample was 141.03 ± 268.80 and in control group was 61.99 ± 40.51. The difference between case and control was not statistically significant (p=0.073). In case group the mean value of Anti-CMV, IgG by MEIA in 2nd sample was 195.69 ± 266.12 and in control group was 61.22 ± 36.15. The difference between case and control was statistically significant (p=0.003).

**Table-VII**

*Distribution of the study subjects by history of respiratory tract infection (n=78) preceding illness (1-4 weeks before)*

| History of Respiratory Tract Infection | Group | | p value |
|---|---|---|---|
| | Case (n=39) | Control (n=39) | |
| Present | 18 (46.2) | 0 (0.0) | <0.001 |
| Absent | 21(53.8) | 39(100.0) | |
| Total | 39(100.0) | 39(100.0) | |

Chi square test (after Yates correction) was done to measure the level of significance.
Odd ratio (95%CI) = 2.86 (2.02-4.03)

Patients with history of respiratory tract infection had 2.86 times more chance to develop GBS than that of control.

Table VII shows the distribution of the study subjects by history of respiratory tract infection. In case group respiratory tract infection was present in 18 (46.2%) cases; 4 (10.2%) cases were CMV positive and absent in 21(53.8%) cases respectively. In control group respiratory tract infection were absent in all 39(100.0%) controls. The difference between case and control was statistically significant (p=<0.001).

**Table-VIII**

*Distribution of the study subjects by history of gastroenteritis (n=78) preceding illness (1-4 weeks before)*

| History of Gastro-enteritis | Group | | p value |
|---|---|---|---|
| | Case (n=39) | Control (n=39) | |
| Present | 11(28.2) | 0 (0.0) | <0.001 |
| Absent | 28(71.8) | 39(100.0) | |
| Total | 39(100.0) | 39(100.0) | |

Chi square test (after Yates correction) was done to measure the level of significance.
Odd ratio (95%CI) = 2.39 (1.80 - 3.17)

Patients with history of gasteroenteritis had 2.39 times more chance to develop GBS than that of control.

Table VIII shows the distribution of the study subjects by history of gastroenteritis. In case group gastroenteritis was present in 11(28.2%) cases; 2(5.1%) cases were CMV positive and absent in 28(71.8%) cases respectively. In control group gastroenteritis was absent in all 39(100.0%) controls. The difference between case and control was statistically significant (p=<0.001).

**Table-IX**

*Distribution of the study subjects by past history of fever (n=78) preceding illness (1-4 weeks before)*

| History of Fever | Group | | p value |
|---|---|---|---|
| | Case (n=39) | Control (n=39) | |
| Present | 12(30.8) | 0(0.0) | <0.001 |
| Absent | 27(69.2) | 39(100.0) | |
| Total | 39(100.0) | 39(100.0) | |

Chi square test (after Yates correction) was done to measure the level of significance.
Odd ratio (95%CI) = 2.44 (1.83 - 3.27)

Patients with history of fever had 2.44 times more chance to develop GBS than that of control.

Table IX shows the distribution of the study subjects by history of fever. In case group fever was present in 12(30.8%) cases and absent in 27(69.2%) cases 01(2.5%) cases was CMV positive. In control group fever was absent in all 39(100.0%) controls. The difference between case and control was statistically significant (p=<0.001).

**Table-X**

*Distribution of the study subject by age (n=78)*

| Age in years | Group | | p value |
|---|---|---|---|
| | Case (n=39) | Control (n=39) | |
| <20 | 8 (20.5) | 8 (20.5) | |
| 20 - 29 | 13 (33.3) | 13 (33.3) | |
| 30 - 39 | 5 (12.8) | 5 (12.8) | |
| 40 - 49 | 10 (25.6) | 10 (25.6) | |
| 50 - 59 | 3 (7.7) | 3 (7.7) | |
| Total | 39(100.0) | 39(100.0) | |
| Mean±SD (Max-min) | 30.82±12.56 (58–12) | 31.00±12.77 (59–12) | 0.950* |

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

Table X shows the distribution of the study subjects by age. In both case and control group all were equal in number in the age group of 20 – 29 years, 40 – 49 years, less than 20 years, 30 – 39 years and 50 – 59 years which were 13 (33.3%) cases,

10 (25.6%) cases, 8 (20.5%) cases, 5 (12.8%) and 3(7.7%) cases respectively. The mean ± SD of case and control groups were 30.82±12.56 and 31.00±12.77 respectively. It was not statistically significant (p=0.950).

**Table-XI**

*Distribution of the study subjects by sex (n=78)*

| Sex | Group | | p value |
|---|---|---|---|
| Fever | Case (n=39) | Control (n=39) | |
| Male | 25(64.1) | 25(64.1) | 1.000 |
| Female | 14(35.9) | 14(35.9) | |
| Total | 39(100.0) | 39(100.0) | |

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

Table XI shows the distribution of the study subject by sex. In both case and control groups male and female were equal in number which were 25(64.1%) and 14(35.9%) respectively. The difference between case and controls was not statistically significant (p=1.000).

**Table-XII**

*Distribution of the cases by CSF study (n=39)*

| CSF Study | Mean ± SD | Min- Max |
|---|---|---|
| CSF cell | 1.95 ± 2.28 | 0.00 - 10.00 |
| CSF sugar | 3.76 ± 1.35 | 0.00 - 7.30 |
| CSF protein | 78.11 ± 94.84 | 0.49 - 390.00 |

Table XII shows the distribution of the cases by CSF study. The Mean ± SD of CSF cell, CSF sugar and CSF protein were 1.95 ± 2.28 mg/dl, 3.76 ± 1.35 cells/cmm and 78.11 ± 94.84 mmol/L respectively.

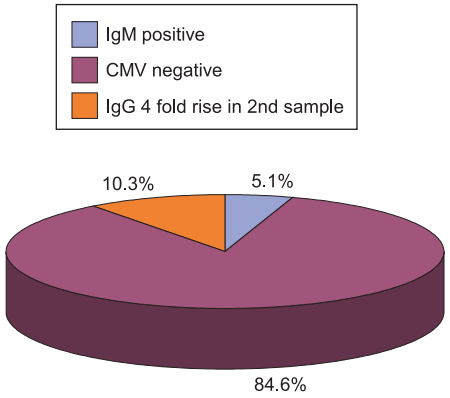


**Fig.-1:** *Distribution of cases by CMV (n=39)*

Figure 1: Shows the distribution of cases by CMV. CMV positive cases by IgM positivity (10.3%), 2 (5.1%) by IgG 4 fold rise in the 2nd sample positive and rest 33 (84.6%) cases were CMV Negative.

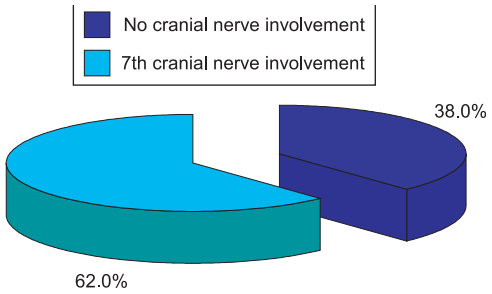


**Fig.-2:** *Distribution of cases by cranial nerves involvement (n=39).*

Figure 2: Shows the distribution of cases by cranial nerve involvement. In 24 (62.0%) cases 7th cranial nerve was involved and in 15(38.0%) cases no cranial nerve was involved.

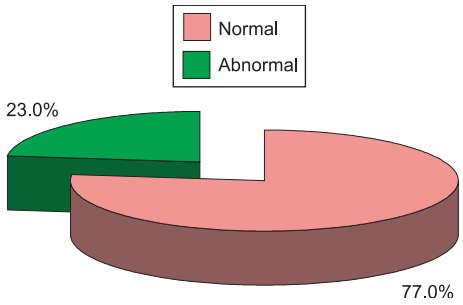


**Fig.-3:** *Distribution of cases by ECG finding (n=39)*

Fig. 3: depicts that near one-quarter 9 cases (23%) had abnormal ECG (6 had sinus tachycardia, 3 had sinus bradycardia) and the rest 30 cases (77%) had normal ECG.

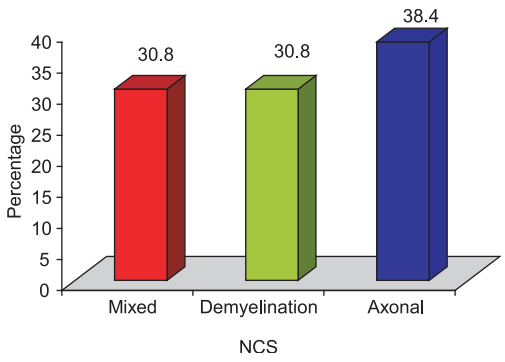


**Fig.-4:** *Distribution of cases by NCS findings (n=39)*

Fig. 4: display the distribution of cases by NCS findings. 12 cases (30.8%) shows demyelination and 15 cases (38.4%) shows axonal and rest 12(30.8%) cases shows mixed demyelinating and axonal type of NCS.

**Discussion:**

Guillain-Barre' Syndrome (GBS) is the most common cause of acute flaccid paralysis[12]. Annual incidence of GBS is approximately 1-3 cases per 100,000 persons in Europe, US and Australia[13].

GBS is an autoimmune disorder of the peripheral nervous system (PNS) with a range of presentations from mild to life-threatening paralysis[14]. The etiology of GBS is unknown, yet several studies link some common exposures as precipitating factors, many of which are commonly seen in the primary care setting. Vaccinations, viral infections, and certain type of food poisoning are examples of antecedent factors of GBS[14]. Due to severity of complications, practitioners need to be aware of what can trigger GBS, who is at risk, how to recognize early signs/ symptoms, what possible prevention exists, and how to educate patients[14].

Gullian Barre syndrome may occur by primary infection or by reinfection or reactivation of CMV[11]. The association of cytomegalo virus infection with Guillian-Barre syndrome needs diagnosis of CMV infection which required at least one of the following laboratory method like serology, specific intrathecal antibody production, virus isolation, direct detection of CMV PP65 antigen in blood, CMV culture, Biopsy, positive specific immunohistochemical staining, Polymerase chain Reaction (PCR) assay etc[8].

A total number of 39 patients with GBS as cases and 39 volunteers, patient's attendants were taken as control who were attended in neurology department at BSMMU during the study period, fulfilling the inclusion and exclusion criteria were included in this study.

The distribution of the study subject by IgGs (Fig.-1) more than 4 fold rise in the 2nd sample was recorded in this study. In the case group 4 (10.3%) cases showed 4 fold rise of IgG and the rest 35 (89.7%) cases showed negative results. In control group 4 fold rise of IgG was absent in all controls which was 39 (100.0%).

The distribution of the study subjects by Anti-CMV IgM was recorded in this study. Anti-CMV IgM antibody was positive in 2 (5.1%) cases and negative in 37 (94.9%) cases. Anti CMV IgM antibody was negative in all 39(100.0%) controls. The difference between case and control was not statistically significant (p=0.474). Similar result was reported by Kimoto K et al. (2006)[15] and added that CMV infections had a role in the development of GBS. Andary (2011)[16] reported that CMV could occur after upper respiratory and flu like illness and it was the most common viral trigger of GBS with the presence of Anti-CMV IgM which was consistent with the present study. Jacobs et al., (1996)[17] found that in CMV-associated GBS, antibodies were common following CMV infection.

The distribution of the patients by CMV positive was recorded in this study. In case group CMV was overall positive in 6 cases of which IgM was positive in 2 cases and 4 fold rise of IgG was positive in 4 cases, rest 33(84.6%) cases were CMV negative. In control group, CMV was negative in all 39(100%) cases. That indicated the relationship between CMV and GBS, which was significantly associated. The difference between case and control group was statistically significant (p=0.034). Similar result was reported by Andary MT (2011)[16] and added that Cytomegalo virus (CMV) infections were the second most commonly reported infections preceding GBS.

The distribution of the study subjects by Anti-CMV IgG Sample-1 was recorded. In case group Anti-CMV IgG (Sample-1) was positive in 33(84.6%) cases and negative in 6(15.4%) cases. In control group Anti-CMV IgG (Sample-1) was positive in 37(94.9%) controls and negative in 2(5.1%) controls. The difference between case and control was not statistically significant (p=0.135). The distribution of the study subjects by Anti-CMV IgG Sample-2 was recorded in this study. In case group Anti-CMV IgG (Sample-2) was positive in 35(89.7%) cases and negative in 4(10.3%) cases. In control group Anti-CMV IgG (Sample-2) was positive in 38(97.4%) controls and negative in 1(2.6%) control. The

difference between case and control group was not statistically significant (p=0.165). The distribution of the study subjects by CMV IgG was recorded in this study. In case group the mean value of Anti-CMV IgG by MEIA in 1st sample was 141.03 ± 268.80 and in control group was 61.99 ± 40.51. The difference between case and control group was not statistically significant (p=0.073). In case group the mean value of Anti-CMV, IgG by MEIA in 2nd sample was 195.69 ± 266.12 and in control group was 61.22 ± 36.15. The difference between case and control group was statistically significant (p=0.003).

The distribution of the study subjects by history of respiratory tract infection was recorded in this study. In case group respiratory tract infection was present in 18(46.2%) cases; 4(10.2%) cases were CMV positive and absent in 21(53.8%) cases. In control group respiratory tract infection were absent in all 100.0% cases. The difference between case and control group was statistically significant (p=<0.001). The distribution of the study subjects by history of gasteroenteritis was recorded in this study. In case group the Gastroenteritis was present in 11(28.2%) cases; 2(5.1%) cases was CMV positive and negative in 28(71.8%) cases. In control group gastroenteritis was absent in all 39(100.0%) controls. The difference between case and control group was statistically significant (p=<0.001). The distribution of the study subjects by past history of fever was recorded in this study. In case group fever was present in 12(30.8%) cases; 1(2.5%) case was CMV positive and negative in 27(69.2%) cases. In control group fever was absent in all 39(100.0%) controls. The difference between case and control group was statistically significant (p=<0.001). Similar result was reported by Andary MT (2011)[16] and mentioned that GBS was considered to be a postinfectious, immune-mediated disease targeting peripheral nerves. Baravelli M et al., (2009)[18] added that up to two thirds of patients report an antecedent bacterial or viral illness prior to the onset of neurologic symptoms. Similarly Nelson L et al., (2009)[19] also reported that respiratory tract infections were most frequently reported, followed by gastrointestinal infections which was consistent with the present study. In another similar study it was mentioned that other systemic illnesses which was manifested by fever have also been associated with GBS[16].

The distribution of the study subjects by age was recorded in this study. In both case and control groups all were equal in number in the age group of 20–29 years, 40–49 years, less than 20 years, 30 – 39 years and 50 – 59 years which were 13 (33.3%) cases, 10 (25.6%) cases, 8 (20.5%) cases, 5 (12.8%) and 3(7.7%) cases respectively. The mean ± SD of case and control groups were 30.82±12.56 and 31.00±12.77 respectively which was not statistically significant (p=0.950). Similar result was reported by Jiang GX[20] and mentioned that GBS had been detected in all age groups, with the syndrome occurring at any time between infancy and old age. In the United States, the syndrome's age distribution seemed to be bimodal, with a first peak in young adulthood (age 15-35 years) and a second, higher one in elderly persons (age 50-59 years). Infants appeared to have the lowest risk of developing GBS[20].

The distribution of the study subjects by sex was recorded in this study. In both case and control groups male and female was equal in number which were 25(64.1%) and 14(35.9%) respectively which was not statistically significant (p=1.000). Similar result was reported by Andary MT (2011)[16] and mentioned that GBS had a male-to-female ratio of 1.5:1; male preponderance was seen especially in older patients. However, a Swedish epidemiologic study reported that GBS rates decrease during pregnancy and increase in the months immediately following delivery[21].

The distribution of the cases by ECG (Fig.-3) was recorded in this study. Near the one-quarter cases 9 (23%) has abnormal ECG (6 had sinus tachycardia, 3 had sinus bradycardia) and the rest 30 (77%) cases had normal ECG. Distribution of cases by cranial nerve involvement which shows (Fig.-2). 15 (38%) had no cranial nerve involvement and 24 (62.0%) had 7th cranial nerve involvement. Distribution of cases by NCS (Fig.-4) in this study shows 12 (30.8%) were demyelinating, 15(38.4%) were axonal and rest 12 (30.8%) cases were mixed type. The distribution of cases by CSF study shows the mean ± SD of CSF cell, CSF sugar and CSF

protein were 1.95 ± 2.28 cells/cmm, 3.76 ± 1.35 mg/dl and 78.11 ± 94.84 respectively.

However, although numerous studies had lead to an accurate description of the GBS related to C. jejuni (Cj-GBS), the GBS associated with primary CMV infection (CMV-GBS) remained poorly documented[22]. Current data were available from just a few studies, most of which had included only a small number of CMV-GBS cases[11]. In these studies, recent primary CMV infection was clearly deûned and the presence or absence of CMV DNA in the blood was not documented[22]. Because of the small number of patients studied, epidemiological characteristics and speciûc prognostic features were not speciûed, and the risk of developing GBS following primary CMV infection was not determined. Visser et al., (1996)[7] in another study had mentioned that cytomegalovirus (CMV) infection accounts for the most common viral triggers of GBS.

This present study strongly showed that Guillain-Barré syndrome (GBS) had great association with cytomegalovirus (CMV) infection.

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# Association of Serum Triglycerides in Patients with Ischaemic Stroke Admitted in Hospital with type-2 Diabetes Patients

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**Abstract:**

***Background and Aims:*** *Diabetes mellitus and dyslipidemia, in particular triglyceridemia pose independent risk factors of stroke. Hypertriglyceridemia implicated in the pathogenesis of ischemic stroke by imparting endothelial dysfunction, oxidative stress and lowering fibrinolytic activity. This study was aimed to explore risk incurred by blood triglyceride level for ischemic stroke in type 2 diabetic patients.* ***Materials and Methods:*** *A total number of 80 [50 with acute ischemic stroke and 30 without stroke] type 2 diabetic patients consecutively admitted in the neurology department, during the period of April to September 2012, fulfilling the recruitment criteria were included in the study. Ischemic stroke was confirmed by CT-scan. Informed written consent from the legal attendant of each patient was obtained. Data regarding clinico-biochemical and images studies were retrieved from patient's record form.* ***Results:*** *Male to female ratio was 1.2:1 of the study subjects. Mean (±SD) age (yrs) was 61.0±10.6 in patients with ischemic stroke (Group I) and 57.0±12.3 in patients without stroke (Group II). Risk factors like BMI, lifestyle, smoking, alcohol intake did not show any statistical significance with incidence of ischemic stroke. Mean (±SD) triglyceride (mg/dl) was 241±56 and 217±102 in Group I and Group II respectively (p=0.024). Eighty eight percent patients had triglyceride 150 mg/dl in Group I and 70 percent in Group II. Triglyceride level (mean±SD, mg/dl) was significantly higher (335±101) in overweight-obese patients (BMI 25 Kg/m$^2$) compared to those (232±68) with normal body weight (BMI<25 Kg/m$^2$). Triglyceride level did not show statistical difference among patients having habit of smoking or not. Mean (±SD) cholesterol (mg/dl, (±SD) was 197±62 and 165±26 in Group I and Group II respectively (p=0.009). Mean (±SD) LDL-c (mg/dl) was 101±45 and 98±42 in Group I (43.8±34.4) compared to Group II (60.2±15.6) (p=0.017). Patients with atherosclerotic changes had significantly higher triglyceride (mean±SD, mg/dl) level (338±155) compared to those without (228±89) (p=0.047).* ***Conclusions:*** *Data concluded that hypertriglyceridemia is relatively common among the diabetic patients even in patients with apparently good glycemic control and possibly incur added risk for ischemic stroke in these patients. However, further studies are needed involving optimum number of patients to substantiate this finding and conclusively comment on the issue and to design effective prevention program to reduce the cerebrovascular morbidity and mortality.*

**Key words***: Ischemic stroke, hypertriglyceridemia, type 2 diabetes mellitus.*

## Introduction:

Stroke is the third most common cause of death in the developed world after cancer and ischemic heart diseases[1]. It may be due to either ischemia or haemorrhage. Among the patients presenting with stroke 85% have sustained cerebral infarction due to inadequate blood flow to part of the brain and remainder are caused by intracerebral hemorrhage. Cerebral infarction is mostly due to thromboembolic disease secondary to atherosclerosis in the major

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extracranial arteries (carotid artery and aortic arch). About 20% of infarctions are due to embolism from heart and a further 20% are due to intrinsic disease of small perforating vessels producing lacunar infarctions. The risk factors for ischemic stroke reflect the risk factor for underlying vascular disease. Perhaps 5% are due to rare causes, including vasculitis, endocarditis and cerebral venous diseases[1].

Number of independent risk factors for ischemic stroke has been implicated. The most common factors include hypertension, diabetes mellitus, smoking, atrial fibrillation, coronary artery disease, and disorders of lipid metabolism. Epidemiologic studies suggest that elevated total cholesterol and low-density lipoprotein cholesterol (LDL-c), as well as low levels of high-density lipoprotein cholesterol (HDL-c) are possible risk factors for ischemic stroke [2,3]. However, consensus regarding the significance of hypertriglyceridemia as an independent risk factor for ischemic stroke still lacking.

Hypertriglyceridemia found to be one of the features of dyslipidemia seen in type 2 diabetes mellitus. Patients with poorly controlled diabetes have higher triglyceride levels than those who have the condition well controlled. Postprandial hyperlipidemia in diabetics appears to be prolonged, which means that the arteries are exposed to atherogenic particles for extended periods of time[4,5]. Postprandial hypertriglyceridemia in diabetic patients was found to produce endothelial dysfunction, oxidative stress due to lipid-derived free radicals, and impairment of endothelium-dependent vasodilatation[6]. Triglyceride-rich lipoproteins, including very-low-density lipoprotein and intermediate-density lipoprotein, in addition to LDL-c particles, become trapped in blood vessel walls and have been demonstrated in human atherosclerotic plaques[7]. Chronic hyper-triglyceridemia was independently associated with endothelial dysfunction in an observational study of patients with normal LDL-c[8]. Increased expression of adhesion cell molecules is considered to be a marker of endothelial cell dysfunction[9]. An increase in cell adhesion molecules has been noted in patients with hypertriglyceridemia[9,10].

Another potential mechanism by which hypertriglyceridemia may contribute to atherosclerosis is through its association with elevated C-reactive protein (CRP). Elevated CRP levels have been found to be associated with elevated triglyceride levels[11]. In humans, carotid intima-media thickness measures are considered reliable markers for early atherosclerosis. Increased carotid intima-media thickness has been found to be associated with an elevation of inflammatory markers, fibrinogen levels and circulating adhesion molecules, each of which has been associated with hypertriglyceridemia[11]. More recently Teno et al(2000) have shown the association of postprandial hypertriglyceridemia with carotid intima-media thickness in a cohort of 61 patients with type 2 diabetes. The investigators found that those with the highest postprandial triglyceride levels had the greatest degree of carotid intima-media thickness, as measured by ultrasound[12].

Hypertriglyceridemia may also contribute to cerebrovascular disease through its effects on thrombosis. This effect is produced by thrombogenic alterations of the coagulation system as well as elevations in plasma viscosity. Hyperviscosity due to hypertriglyceridemia may contribute to endothelial dysfunction, tissue ischemia and chylo-micronemia[13]. This effect is greater than that for LDL-c, supporting the greater contribution of triglycerides to plasma viscosity[14]. Elevated levels of triglycerides (as well as fibrinogen, total protein, LDL-c and total cholesterol) correlated positively and independently with elevated plasma viscosity [13] and hypertriglyceridemia thus increase the risk of ischemic stroke by inducing a prothrombotic state through its effects on coagulation and plasma viscosity. The Copenhagen City Heart prospective Study on 19,698 men and women demonstrated strong linear association between nonfasting triglyceride levels and cerebral ischemic events like ischemic sclerosis and transient ischemic attack[15,16].

The relation between high triglyceride level and ischemic stroke is not clear as it is in coronary heart disease. The role of high concentration of serum triglyceride as a risk factor for stroke is still undecided at the present time. Patient with uncontrolled diabetes usually have high triglyceride level and diabetes itself is a risk factor for stroke.

There are limited studies on risk factor analysis of stroke in Bangladesh. Present study is designed to evaluate, is there any relationship of hypertriglyceridemia with ischemic stroke in diabetic patient. Knowledge obtained from this study may help in recognizing the magnitude of the disease problem, and to take necessary measures to treat ischemic stroke patient with diabetes and hypertrigiyceridemia in the community. More over it will provide base line information for further research for further study.

**Materials and Methods:**

This observational study was carried out in the department of Neurology, BIRDEM General Hospital during the period of April–September 2012. Patients with acute ischemic stroke with type 2 diabetes mellitus consecutively admitted in the department of neurology, BIRDEM General Hospital, and fulfilling the recruitment criteria were included in the study. A representative number of type 2 diabetic patients admitted in the hospital without stroke served as controls.

**Recruitment criteria**

*Inclusion criteria*

Type 2 diabetic patients, age range 20-80 yrs admitted in the hospital with clinical feature of acute ischemic stroke, confirmed by imaging study (CT/ MRI scan), their legitimate attendant(s) consented for entry in the study being detailed brief about its purpose and nature, were recruited.

*Exclusion criteria*

Type 2 diabetic patients with signs of previous or recent hemorrhagic stroke, on lipid lowering drug, taking drug associated with hypertriglyceridemia (corticosteroid, diuretics, Beta blocker), having other medical condition eg. chronic renal disease, hepatocellular disease, nephrotic syndrome, hypothyroidsm and patients attendant not consented were excluded.

**Operational definitions for the study**

*Hypertriglyceridemia*

The definition of hypertriglyceridemia is based on a classification in the Third report of the National Cholesterol Educational Program and the Adult Treatment Panel (NCEP-ATP III, USA)[17]. Classification of serum triglyceride levels, according to the NCEP-ATP III: Normal - 150 mg/dl; Border line high - 150 to 199 mg/dl; High- 200 to 499 mg/dl and Very high- 500 mg/dl.

*Ischemic stroke*

Stroke is defined by the World Health Organization as a clinical syndrome consisting of 'rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin[18]. Ischemic stroke or Cerebral infarction is mostly due to thromboembolic disease secondary to atherosclerosis in the major extracranial arteries (carotid artery and aortic arch)[1]

*Type 2 diabetes mellitus*

Diabetes is a clinical syndrome characterised by hyperglycemia due to absolute or relative deficiency of insulin. In type 2 diabetes mellitus there is a combination of resistance to the action of insulin in liver and muscle together with impaired pancreatic beta cell function leading to relative insulin deficiency[19].

*Detailed procedure*

Data regarding, sex and risk factors like BMI, life style, habit of smoking, betel nut chewing and alcohol intake, biochemical variables (fasting and post-prandial blood glucose and lipid profile), were recorded using predesigned semi-structured questionnaire. Details about the nature and purpose of the study were briefed to the patients and/ or their legitimate attendant and written consent was obtained from participant/ attendant. Basic principles of research ethics according to 52$^{nd}$ WMA declaration of Helsinki'2000 & CIOMS guidelines was maintained during the research processes.

*Outcome variables*

Age, sex, obesity, life style and, habit of smoking, betel nut and alcohol intake, doppler study of carotid vessels, triglyceride.

*Statistical analysis*

Data were expressed as mean±SD, range (minimum-maximum) and number (percent) as appropriate. Statistical analyses were performed using Statistical Program for Social Science (SPSS)

for Windows, Version 16.0 (SPSS, Inc. Chicago III).Statistical tools Unpaired Student's-'t' test and Chi-squared test (Fisher Exact) were used to calculate statistical difference between groups as applicable. A p value <0.05 was taken as level of significance.

**Results:**

Male female distribution of the study subjects is shown in Figure 1. Of the 50 subjects in Group I male subjects constituted 56% and female 44% and in Group II the distribution is 53.3% and 46.7%. This distribution does not show any significant association.

Mean (±SD) age (yrs) is 61.0±10.6 and 57.0±12.3 in Group I and Group II respectively (p=0.128). Distribution of subjects in percent in the two groups is shown in Figure II. Around sixty percent of the study subjects in the two groups are in age groups of 50-70 yrs. The distribution does not show significant association.

Clinico-biochemical data is shown in Table I. Age, BMI and blood pressure of the two groups does not show any statistical significance. Serum triglyceride and total cholesterol level are significantly high in the Group I compared to Group II (p=0.024 and 0.009 respectively). LDL-c in the two groups do not show any significant difference (p=0.828). HDL-c level is significantly lower in the Group I compared to the Group II (p=0.017). (Table I).

Distribution of the subjects with or without known risk factors in the two groups is shown in Table II. None of the subjects in the two groups has positive history of drinking alcohol. Body weight, physical activity level, smoking and betel nut chewing do not show any significant association with ischemic stroke. In Group I 88% of the subjects with acute ischemic stroke has triglyceride level above the cut-off compared to 70% in the Group II which also do not show significant association (p=0.079) (Table II).

Study variables are analyzed on the basis of serum triglyceride status (Table III). Sedentary life style and presence of carotid artery atherosclerotic changes are significantly associated with hypertriglyceridemia (p=0.006 and 0.004 respectively). Serum triglyceride level (mean±SD) is also looked into on the basis of presence or absence of risk variables. In the Group I subjects having carotid atherosclerotic changes and overweight-obesity (BMI 25 Kg/m$^2$) has significantly high level of serum triglyceride level (p=0.047 and 0.035) (Figure IIIA and E respectively).

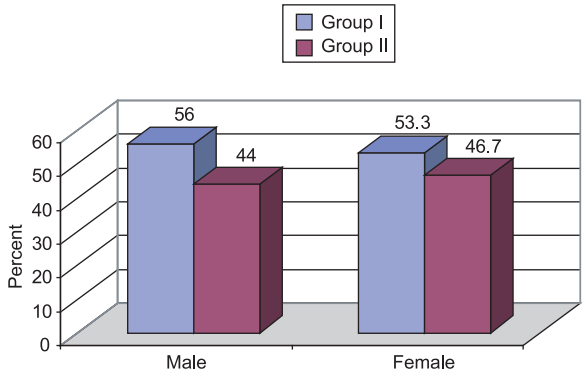


**Fig.-1:** *Distribution (percent) of male and female subjects of the two groups (Group 1, acute ischemic stroke and Group II, without ischemic stroke).*

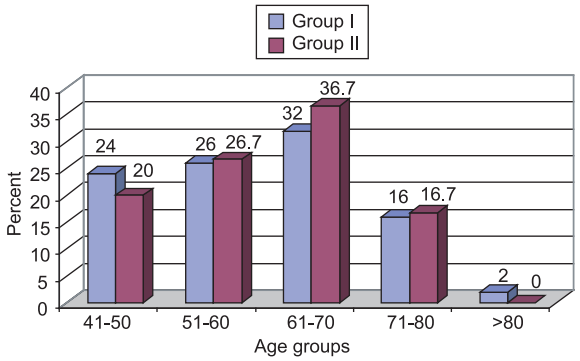


**Figure 2:** *Distribution (percent) of subjects of the two groups (Group 1, acute ischemic stroke and Group II, without ischemic stroke) in different age groups.*

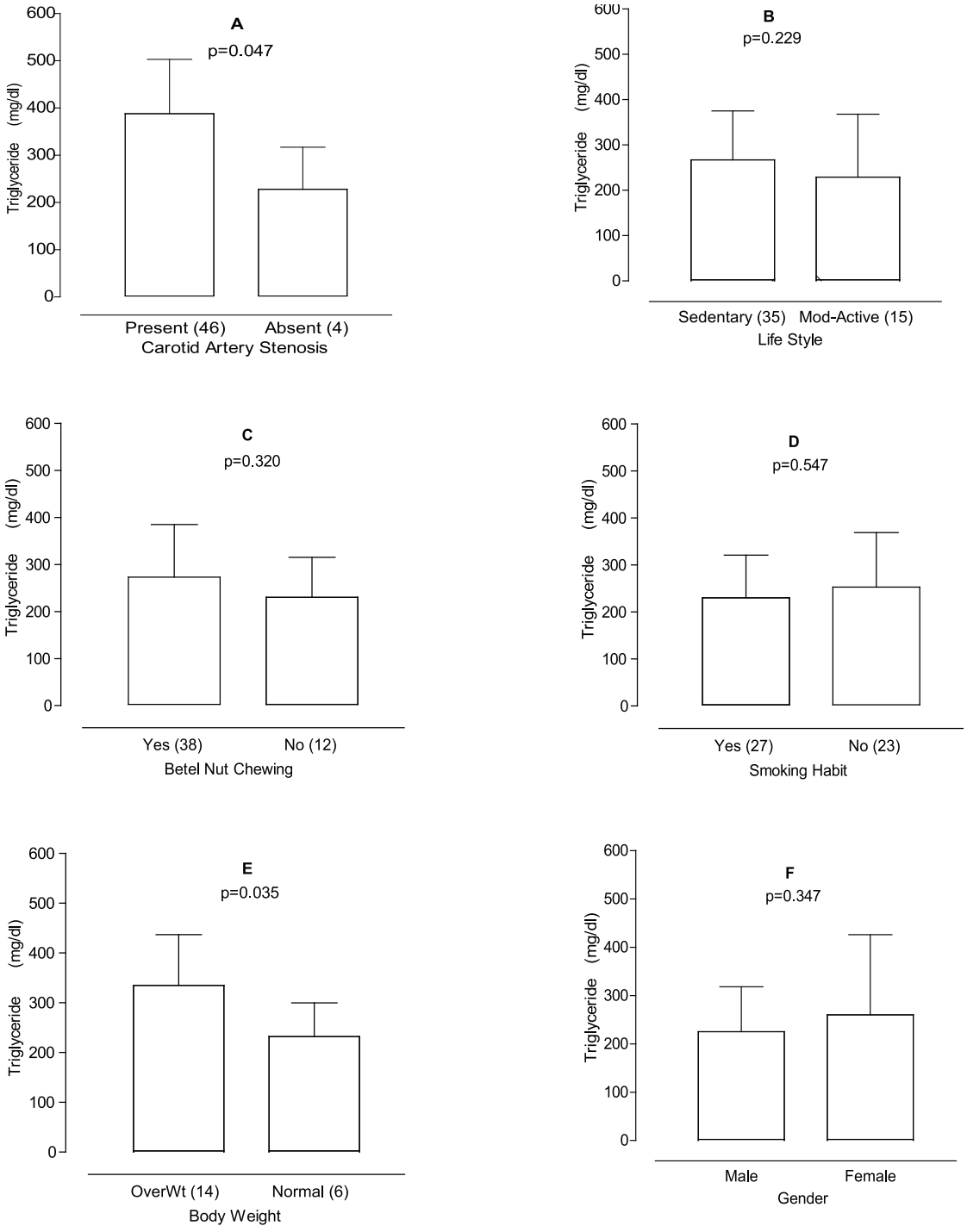


**Fig.-3:** *Serum triglyceride (mg/dl) is shown in acute ischemic stroke patients with T2DM on the basis of carotid artery stenosis (A), life style (B), habit of betel nut chewing (C) and smoking (D), body weight (E) and gender (F).*

**Table-I**

*Clinico-biochemical variables of the study subjects*

| Variables | Group I (n=50) | Group II (n=30) | P value |
|---|---|---|---|
| Age (yrs) | 61.0±10.6 | 57.0±12.3 | 0.128 |
| BMI (Kg/m$^2$) | 25.7±2.4 | 24.8±3.2 | 0.157 |
| Blood pressure (mmHg) | | | |
| Systolic | 135±11 | 140±13 | 0.079 |
| Diastolic | 86±8 | 83±10 | 0.144 |
| Triglyceride (mg/dl) | 241±56 | 217±102 | 0.024 |
| T cholesterol (mg/dl) | 197±62 | 165±26 | 0.009 |
| LDL-c (mg/dl) | 101±45 | 98±42 | 0.828 |
| HDL-c (mg/dl) | 43.8±34.4 | 60.0±15.0 | 0.017 |

Data is expressed as mean±SD. Unpaired Student's-'t' test is performed to calculate statistical difference between two groups. P<0.05 is taken as level of significance.

**Table-II**

*Distribution of the study subjects in the two groups on the basis of risk variables*

| Variables | Group I | | Group II | | p value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Body weight | | | | | |
| *Over weight-obese* | 14 | 70.0 | 18 | 60.0 | 0.470 |
| *Normal body weight* | 6 | 30.0 | 12 | 40.0 | |
| Smoking | | | | | |
| *Yes* | 27 | 54.0 | 20 | 66.7 | 0.265 |
| *No* | 23 | 46.0 | 10 | 33.3 | |
| Betel Nut chewing | | | | | |
| *Yes* | 38 | 76.0 | 19 | 63.3 | 0.225 |
| *No* | 12 | 24.0 | 11 | 36.7 | |
| Life style | | | | | |
| *Sedentary* | 35 | 70.0 | 23 | 76.7 | 0.517 |
| *Moderately active* | 15 | 30.0 | 7 | 23.3 | |
| Serum triglyceride | | | | | |
| *High (>150 mg/dl)* | 44 | 88.0 | 21 | 70.0 | 0.079 |
| *Normal (<150 mg/dl)* | 6 | 12.0 | 9 | 30.0 | |

Data are expressed as number (percent).
Chi-squared test is performed to calculate statistical association for ischemic stroke. P<0.05 is taken as level of significance.
Over weight-obese, BMI 25 kg/m$^2$; Normal body weight, BMI <25 Kg/m$^2$

**Table-III**

*Distribution of subjects with acute ischemic stroke (Group I) on the basis of different risk variables*

| Variables | Serum triglyceride (mg/dl) | | P value |
|---|---|---|---|
| | >150 mg | < 150 mg | |
| | N (%) | N (%) | |
| Gender | | | |
| *Male (n=28)* | 24 (87.7) | 4 (14.3) | 0.683 |
| *Female (n=22)* | 20 (90.9) | 2 (9.1) | |
| Body weight | | | |
| *Overweight-obese (n=14)* | 12 (85.7) | 2 (14.3) | 0.989 |
| *Normal (n=6)* | 5 (83.3) | 1 (16.7) | |
| Smoking | | | |
| *Yes (n=27)* | 24 (88.9) | 3 (11.1) | 0.898 |
| *No (n=23)* | 20 (87) | 3 (13) | |
| Betel nut chewing | | | |
| *Yes (n=38)* | 35 (92.1) | 3 (7.9) | 0.141 |
| *No (n=12)* | 9 (75) | 3 (25) | |
| Physical activity | | | |
| *Sedentary* | 34 (97.1) | 1 (2.9) | 0.006 |
| *Moderately active* | 10 (75) | 5 (25) | |
| Carotid artery stenosis | | | |
| *Yes (n=46)* | 43 (93.5) | 3 (6.5) | 0.004 |
| *No (n=4)* | 1 (25) | 3 (75) | |

Data are expressed as number (percent).
Chi-squared test is performed to calculate statistical association for ischemic stroke. P<0.05 is taken as level of significance. Over weight-obese, BMI 25 kg/$m^2$; Normal body weight, BMI <25 Kg/$m^2$

**Discussion**

This observational study was carried out with an aim to explore the association, if any, between triglyceride and ischemic stroke in diabetic patients. A total number of 50 type 2 diabetic patient with acute ischemic stroke admitted in the department of Neurology, BIRDEM General Hospital. Thirty (30) T2DM patients without ischemic stroke served as controls.

The present study demonstrated that about 60% of cases in both the croups are in 50-70 years age group. Although in an earlier study it is reported that 36.2% developed stroke in more than 60 years[20]. Mean age (61.0±10.6) of the patients with ischemic stroke which is consistent with previous reports[11,21]. However, some authors reported relatively lower mean age (yrs) at the time of the events [22,23].

The incidence of ischemic stroke in the present study is 56.0% and 44.0% in male and female respectively. Male to female ratio is 1.3:1 in ischemic stroke. This observation is consistent with number of studies which showed similsr male to female ratio[8,19,24]. Although, male preponderance was high (4.9:1) compared to their female counterpart in one report [25].

In the present study 70.0% were overweight (BMI 25 kg/$m^2$) in Group I and 60.0% in Group II. More than a half (54.0%) of the patients was smoker in Group I and 66.7% in Group II. More than three fourth (76.0%) of the patients had habit of betel nut chewing in Group I and relatively low (63.3%) in Group II. Sedentary lifestyle was 70.0% observed in Group I and 76.7% in Group II. These features did not show any statistical association which indicated that the risk factors were almost consistent between two groups. Marked hypertriglyceridemia in type 2 diabetes mellitus and presence of other predisposing factors which include chronic insulin deficiency, age, obesity, sedentary lifestyle,

medications for other comorbid conditions were reported earlier[21]. Diabetes mellitus, hypertension, dyslipidemia, smoking, family history of CAD and age more than 60 years were considered as conventional risk factors for ischemic stroke. History of smoking was present in 24% cases.

Hypertriglyceridemia (>150 mg/dl) was present in almost ninety percent (88.0%) of the patients of Group I and 70.0% in Group II and significantly higher mean triglyceride level in Group I compared to the counterpart Group II (p=0.024). However in one study relatively low mean triglyceride level (145.0±85.3 mg/dl) in the ischemic stroke group compared the controls (241.0±103 mg/dl)[23]. In the present study serum total cholesterol is also found to be significantly higher (p=0.009) in the ischemic stroke group. However, LDL-c was almost similar in the two groups. But HDL-c was significantly lower (p=0.017) in the ischemic stroke group (Table I). One particular study demonstrated significantly higher level of total cholesterol (mg/dl) [217.7±49.7 vs 202.3±45.8; p=0.001] and lower HDL-c [41.5±12.1 vs 45.9±17.7; (p=0.010) in stroke/TIA patients compared to the control[21]. The authors, however, also demonstrated significantly higher LDL-c in the ischemic stroke group. Although findings in the present study were consistent regarding lipid levels in the other reports [9,11].

Proportion of male and female patients with hypertriglyceridemia (>150 mg/dl) was relatively high and almost similar frequency [85.7% and 90.9% respectively]. The mean triglyceride was found 225.07±93.09 mg/dl in male and 260.32±166.43 mg/dl in female patients, which was almost similar between male and female patients. Similar observations regarding the triglyceride (TG) level between male and female were also demonstrated in two different reports [13,26].

Height and weight could be measured only 20 patients in the present study. Out of which 14 patients were overweight-obese (BMI >25 kg/m$^2$) and 6 patients had normal body weight (BMI<25 kg/m$^2$). The mean triglyceride level was found 335.0±101.5 mg/dl in over weighted patients and 231.6±67.9 mg/dl in normal body weight patients, which was significantly higher in over weight-obese patients (p=0.035, Figure IIIE). This was supported in the study reported previously who have also observed marked hypertriglyceridemia associated with obesity [5].

Habit of smoking and betel nut chewing in the present study did not show any statistical association with ischemic events and those having the risk factor present also had almost similar level of serum triglyceride level (Table III and Figure III). These features are supported by other authors.

The present study demonstrated that 97.1% of the patients with ischemic stroke had sedentary life and 66.7% of them had hypertriglyceridemia. Although serum triglyceride level between patients having sedentary lifestyle and moderately activity level did not show statistical difference. Although earlier it was suggested suggested that hypertriglyceridemia indicates the presence of predisposing factors like sedentary lifestyle and/or late expression of other genetic lipid disturbances[5].

Of the total ischemic stroke subjects atherosclerotic changes in carotid vessels was observed in 46 subjects and of these 93.5% had hypertriglyceridemia. However, of the 4 subjects who had no atherosclerotic changes only 1 had hypertriglyceridemia and this distribution showed significant association (p=0.004). Triglyceride level was also significantly high in those with presence of atherosclerotic changes compared to the counterpart (p=0.047) (Figure IIIA). This observation possibly signifies that hypertriglyceridemia possibly accentuate progression of atheroscrerotic changes in carotid vessels and incur additional risk for ischemic stroke in the diabetic patients.

**Conclusions:**

Data concluded that hypertriglyceridemia is relatively common among the diabetic patients even in patients with apparently good glycemic control and possibly incur added risk for ischemic stroke in these patients. However, further studies are needed involving optimum number of patients to substantiate this finding and conclusively comment on the issue and to design effective prevention program to reduce the cerebrovascular morbidity and mortality.

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# Extended Endonasal Solo Endoscopic Approach for the Resection of Craniopharyngiomas

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**Abstract:**

***Background:*** *Extended endonasal solo endoscopic approach for the non-pituitary lesions of the sellar and suprasellar regions are not new in the field of neurosurgery. Following endoscopic surgical approach of the pituitary adenoma, endoscopic neurosurgeon is eager to develop the skill for non-pituitary sellar & suprasellar lesions. Common sellar & suprasellar lesions are pituitary adenoma, craniopharyngioma, tuberculumselle meningioma and suprasellar germinoma.* ***Objective****: Traditional transsphenoidal approach gives exposure to the pituitary fossa, whereas extended approach provides exposure to the optic nerve, chiasm, acom complex and basal frontal lobe ,mammillary body, mid brain and laterally to the cavernous sinuses.* ***Material & method:*** *From November 2007 to March 2012, 12 cases of done by extended endonasal solo endoscopic approach among 12 cases of craniopharyngiomas. Patient's history, clinical findings, pre-operative and post-operative visual acuity, visual field and radiological data were collected and analyzed. All patients underwent solo endoscopic extended transsphenoidal approach with or without nasoseptal flap technique for closure. Most of the patients were given lumbar drain as a treatment for CSF leak.* ***Result:*** *All patients were of age group of 10 to 60 years. Male were 8 (66.67%), female were 4 (33.33%) in number. Gross total removals were done in 7 cases out of 12 (58.33%) craniopharyngiomas and subtotal removal done in 5 (41.67%) cases. Visual acuity and field of vision were improved in all cases of craniopharyngiomas. One case (8.33%) of craniopharyngioma had prolong period of unconsciousness probably from hypothalamic disturbance. CSF leak developed in 2 (16.67%) cases. Patients with craniopharyngioma were required thyroxin and cortisol for replacement. Permanent diabetes insipidus developed in 5 cases (41.67%). Three patients required permanent CSF diversion via a ventriculoperitoneal shunt after documentation of postoperative HCP. There was one case of chemical meningitis, and two cases confirmed bacterial infections. Craniopharyngioma can be successfully resected via a purely endoscopic, endonasal approach. Craniopharyngioma have a higher rate of perioperative hydrocephalus and postoperative CSF leak compared with other tumor types in the same area.* ***Conclusion:*** *Extended transsphenoidal approach is an excellent alternative of skull base approach for the removal of most of the craniopharyngioma.The endoscopic endonasal route provides a good exposure, especially of the sub-chiasmatic and retro-chiasmatic areas, as well as of the stalk–infundibulum axis and the third ventricle chamber. It gives better visualization, improved postoperative visual outcome for less manipulation and low complication then craniotomy. However CSF leak and diabetes insipidus is common known complications which have to be manage promptly and appropriately.*

***Abbreviation:*** *CSF (cerebrospinal fluid), D I (diabetis insipidus), HCP(hydrocephalus)*

## Introduction:

Craniopharyngioma is a benign epithelial tumors of the seller region but can have significant neurological and endocrinological consequences and may require treatment that will cause further morbidity[1]. As craniopharyngioma grow, it can cause significant

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neurological complications, including visual loss, pituitary insufficiency, and hypothalamic damage, and recurrence following surgery. The first description of a craniopharyngioma was credited to Zenker, who made this observation in 1857[1,2]. Following this, Mott and Barrett, in 1899, documented the occurrence of these tumors and postulated that they arose from the hypophyseal duct or Rathke pouch[3]. This was subsequently partially confirmed in 1904, when Erdheim described the tumors histologically and suggested that they arose from remnants of the Rathke duct[3,4]. Finally, in 1932, Cushing introduced the term "craniopharyngioma," which has been widely used thereafter.

The incidence of newly diagnosed craniopharyngioma is 0.13 to 2.0 persons per 100,000 population per year. Distribution by age is bimodal, with the peak incidence in children in between 5-14 years and in adults in between 50-75 years[5]. Craniopharyngioma account for 1-3%of all brain tumors, and half of these tumors occur in childhood. Craniopharyngioma account for 5-10% of brain tumors in children.No sex predilection exists, and they equally occur in males and females[5,6].

The clinical presentation can include a wide range of symptoms, which depend on the location of the tumor and involvement of adjacent structures[7]. Headache is the most common presenting symptom, followed by endocrine deficiencies and visual disturbances. Headache is usually due to either the tumor's mass effect or hydrocephalus (from obstruction of the foramen of Monro, third ventricle, or aqueduct of Sylvius), which occurs in 15-30% of patients[6,7].

Endocrine disturbances are related to direct compression from the tumor. Of the endocrine deficiencies, the most common is growth hormone (75%), followed by gonadotropin (40%), thyroid-stimulating hormone (25%), and corticotropin (25%) hormones. Growth failure can be seen in up to 93% of children with craniopharyngioma and is related to either growth hormone deficiency, hypothyroidism, or both. Adults have more varied presentation and may develop sexual or menstrual dysfunction. Eighty-eight percent of men experience decreased sex drive, while 82% of women have amenorrhea. Other endocrine dysfunction may lead to precocious puberty and obesity[8].

Large tumors in adults can cause psychiatric symptoms, memory loss, apathy, incontinence, depression, and hypersomnia. Long-standing cognitive deficits and profound memory loss have been reported and suggest a worse prognosis. Visual deficits are caused by compression of the optic chiasm from supraseller tumor growth. Classically, the tumor presents as a Bitemporal hemianopia, but it may also manifest as homonymous hemianopia, scotoma, papilloedema or optic atrophy[9].

Craniopharyngioma surgically divided into 3 groups: seller, prechiasmatic, and retrochiasmatic. Seller-located tumors may be supraseller (75%), infraseller (21%), or intraseller (4%). According to the grade of involvement of the third ventricle, we identified three main ventricular growth patterns: (1) stalk–infundibulum; (2) infundibulum–ventricular chamber; (3) stalk–infundibulum–ventricular chamber. These tumors occasionally grow into the third ventricle, causing hydrocephalus[10,11].

The classification scheme divides tumors according to their supraseller extension: Type I is preinfundibular; Type II is transinfundibular (extending into the stalk); Type III is retroinfundibular, extending behind the gland and stalk, and has 2 subdivisions (IIIa, extending into the third ventricle; and IIIb, extending into the interpeduncular cistern); and Type IV is isolated to the third ventricle and/or optic recess and is not accessible via an endonasal approach[11,12].

The arterial supply is usually from the anterior cerebral and anterior communicating arteries or from the internal carotid and posterior communicating arteries[12].A craniopharyngioma does not receive blood supply from the posterior circulation, unless it is parasitized from the floor of the third ventricle. As these tumors enlarge, they may elevate and infiltrate the optic chiasm as well as the hypothalamic region. Occasionally, they extend into the pituitary fossa or posteriorly to the ventral pons, and, rarely, they invade the basal ganglia or the brain parenchyma[13].When predominantly in the sella, these tumors erode the bony floor and enlarge the sella.

**Methods:**
From November 2007 to March 2013, 12 cases of done by extended endonasal solo endoscopic approach among 12 cases of craniopharyngiomas. Patient's history, clinical findings, pre-operative and post-operative visual acuity, visual field and radiological data were collected and analyzed. All patients underwent solo endoscopic extended transsphenoidal approach with or without nasoseptal flap technique for closure. Most of the patients were given lumbar drain as a treatment for CSF leak.

**Results:**
There were 12 patients retrospectively. Among them 8 patients were male, 4 were females. Age of the patients ranged from 10 years to 60 years, with a mean age of 34.5 years.

All the patients complained of headache and vomiting. Anosmia and personality or behavioral changes were the next common manifestations. Visual impairment was found in 8cases (66.67%) associated with primary optic ataphy.All patients underwent preoperative and postoperative CT scan and/ or MRI of brain. Maximum tumor diameter was 4.5 cm and mean diameter was 3.42 cm.

Retrochaismaticcraniopharyngioma in 6 patients (50.00%), subchaismatic in 3 patients (25.00%) andPrechaismatic in 1 patient (8.33%), Pre and Retrochaismatic in 2 patients (16.67%) (Table-I).In all the cases surgery was performed with the help of endoscopic endonasal instrumentation.

**Table-I**
*Types of Craniopharyngioma*

| Name of disease | | Number of Cases | Percentage |
|---|---|---|---|
| Craniopharyngioma | Retrochaismatic | 6 | 50.00% |
| | Sub chaismatic | 3 | 25.00% |
| | Prechaismatic | 1 | 8.33% |
| | Pre and Retrochaismatic | 2 | 16.67% |
| Total | | 12 | 100% |

**Extent of Resection:** Extent of resection was determined using pre-operative and post-operativevolumetric analysis of CT scanimages. The comparison was performed by chief surgeon. Evaluation of the series has shown that 7 (58.33%) of the 12 patients underwent at least gross-total resection(Table-II). Five cases (41.67%) of the patients underwent sub-total. All the twelve patients were followed-upwith early postoperative CT scan (Figure 1(a,b,c,d)) and neurological evaluation.

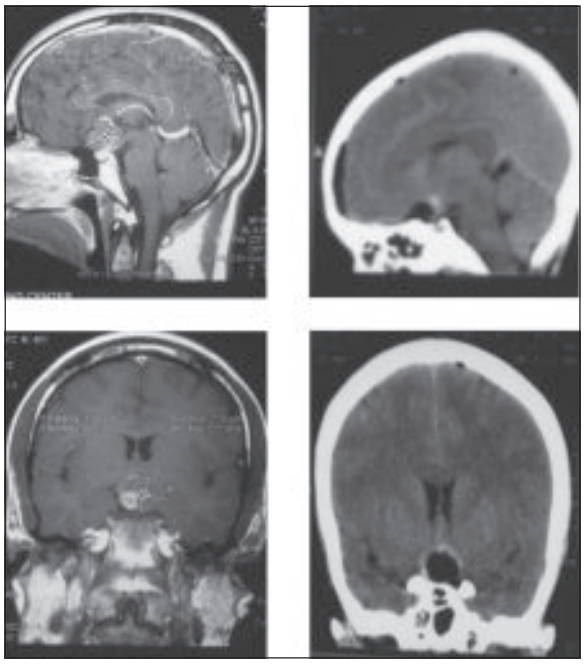

**Fig.-1:** *(a) suprasellercraniopharyngioma(pre op), (b) suprasellercraniopharyngioma(post op), (c) suprasellercraniopharyngioma(pre op), (d) suprasellercraniopharyngioma (post op).*

The follow up period ranged from 7 month to 16 months. No recurrence of tumor was found within this short period of follow up. CSF leak was found in two cases. There is no mortality in twelve cases. Two patients developed meningitis among them one patient developed CSF rhinorrhea along with meningitis. This patient was treated by antibiotic therapy and lumbar drain for CSF leak. Small subdural hygroma was developed in one case and small amount of tumor bed hematoma was seen in one case which resolved over time as was evidenced in later scan. Steven Johnson's syndrome was developed in one case following phenytoin therapy. Outcome was good having GOS 5 in 8 patients (66.67%), GOS 4 in 3 patients (25%) and GOS 3 in 1 (8.33%) patient during the follow up period (Table-II).

**Table-II**

*Shows size, Extent of tumour removal, complication and outcome of craniopharyngioma.*

| No. of Cases | Size of tumour | Extent of tumour removal | Complications | Outcome |
|---|---|---|---|---|
| 1. | 3x2x3cm | Gross total | Permanent DI, Confusion,Dependent feeding | GOS 3 |
| 2. | 4x3x4cm | Gross total | Permanent DI , Food refusal | GOS 4 |
| 3. | 4x3x4cm | Gross total | Confusion, Irrelevant talkVP Shunt, Surgery done for hydrocephalus | GOS 5 |
| 4. | 2.5x3x4cm | Sub Total | Permanent DI | GOS 5 |
| 5. | 3x3x3cm | Gross total | NIL | GOS 5 |
| 6. | 4x3x3 cm | Gross total | C.S.F. leak | GOS 5 |
| 7. | 4.5x3x3.5cm | Sub total | Permanent DI | GOS 5 |
| 8. | 3x3.5x3.5cm | Sub total | Hyponatremia | GOS 5 |
| 9. | 2.5x2.5x3cm | Sub total | Pneumocephalus | GOS5 |
| 10. | 3x3x3cm | Sub total | Tumorbedhaematoma | GOS5 |
| 11. | 3x3x3cm | Gross total | C.S.F. leak | GOS 4 |
| 12 | 2.5x 2x3 cm | Gross total | Permanent DI | GOS 4 |

Postop visual outcome: Visual improvement was satisfactory. Postoperative visual acuity and visual field were improved in 8 cases (66.67%) (Table-III)(Figure 2 & Figure 3).The visual outcome (for both acuity and fields) was better in younger patients and those with a shorter duration of symptoms. Patients with lesser degrees of preoperative visual acuity compromise had better postoperative visual acuity outcome. However, the severity of preoperative visual field defects did not seem to predict postoperative field outcome, and even patients with severe preoperative field defects often had striking postoperative improvement.

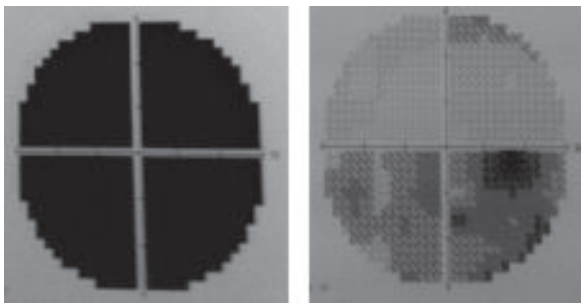

**Fig.-2:** *Pre op (A) and Post op (B) picture of visual field of right eye showing significant improvement.*

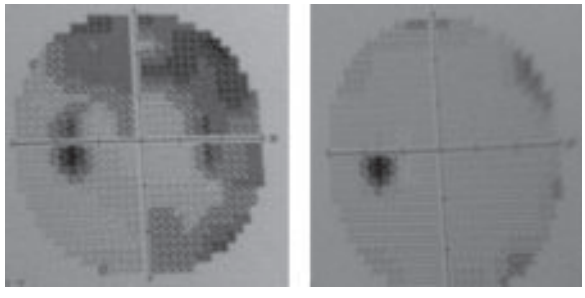

**Fig.-3:** *Pre op (A) and Post op (B) picture of visual field of left eye showing significant improvement.*

**Table-III**

*Preoperative & Postoperative Visual Status*

| Pre-operative Visual status | No. of Cases | Percent | Post-operative Visual status | No. of Cases | Percent |
|---|---|---|---|---|---|
| Bi temporal field defect | 4 | 33.33% | Improved | 8 | 66.67% |
| Unilateral blindness and Contra lateral temporal field defect | 6 | 50.00% | Not improved/ Static | 2 | 16.67% |
| Bilateral blindness | 2 | 16.67% | Deteriorated | 2 | 16.66% |
| Total | 12 | 100% | Total | 12 | 100% |

**Endocrine outcome:**

Preop endocrine presentation: Typical endocrinological findings were hypocortisolism, hypothyroidism and hypogonadism were found in most of the cases.

Postop endocrine outcome: Postoperative anterior pituitary dysfunction improved in 4 cases (33.33%) out of 12 cases. There were 100% cases of temporary DI and about 5% cases of permanent DI.

Complications:PermanentDI developed in 5 patients (41.67%), Pneumocephalus in 3 patient (25.0%), Small amount of tumor bed hematoma in 1 patient (8.33%), Hyponatremia in 4 patients (33.33%), Hydrocephalus in 2 patients (16.67%) for which V-P shunt were done.

**Discussion:**

The extended transphenoidal approach extends operative exposure beyond the sella by removing the tuberculum sellae and a portion of the planum sphenoidale. The advantages of the extended transphenoidal approach over a traditional craniotomy are the avoidance of frontal or temporal lobe retraction or sylvian fissure dissection and the potential associated brain injury[14].

Approximately 10% of all transcranial cranial base procedures result in some form of retraction injury to the brain. However, it has generally been thought that an enlarged sella, secondary to the lesions extension, was required to safely reach a suprasellar lesion through a transphenoidal approach[15].

In our study all 12 patients underwent a detailed neuroophthalmological examination before and after surgery. Eight (66.67%) of these patients had complete resolution of their visual defect and 2 (16.66%) had improvement but not complete resolution. Two patient's deficit deteriorated.

In an international study by Amin B. Kassam et al, showed that all of 16 patients underwent a detailed neuroophthalmological examination before and after surgery[10]. The conditions of 2 patients without preoperative visual deficits were unchanged postoperatively. The remaining 14 patients had progressive visual deficits preoperatively. Six (43%) of these patients had complete resolution of their visual defect, and seven (50%) had improvement but not complete resolution. One patient's deficit remained stable. One patient had visual worsening 4 days after surgery secondary to hydrocephalus. His vision improved following the placement of a VP shunt[16].

In an international publication of endocrinological results of 30 patients of craniopharyngioma (Honegger et al. 1999) treated transcranially developed postoperative diabetes insipidus in 60% cases, adrenal failure in 53.3% and hypothyroidism in 36.7% cases[17].

Microscope-based removal of purely suprasellar craniopharyngiomas and meningiomas has been associated with a 20 to 33% rate of CSF leak. For craniopharyngiomas, postoperative rates of DI and panhypopituitarism occur in roughly 70% cases. In our study permanent DI developed in 5 cases (41.67%)out of 12, using the endoscopic endonasal approach[18,19].

We did gross total resection of 6 cases (50%) of the craniopharyngiomas with an overall risk of postoperative CSF leak of 4 cases (33.33%).

We found that the visualization provided by the endoscope is outstanding for the extended approach to purely suprasellar pathology. This advantage can potentially minimize the risk of morbidity to vital neurovascular structures and also decrease the risk of CSF leakage because closure is more secure, aided by improved visualization[20,21].

Despite the minimally invasive approach and the use of the endoscope, these endoscopically treated cases are not without morbidity. However, removal of these lesions using a traditional microscope-based transcranial or transphenoidal route also has a potentially high morbidity and mortality rate. The success of this maneuver requires meticulous closure with dural graft inlay, either fascia lata or Dura-Guard, rigid buttressing with either vomer or a metalplate and the use of sealants, such as fibrin glue[22].

**Conclusion:**

Extended transphenoidal approach is an excellent alternative of skull base approach for the removal of selected group of the craniopharyngioma.The endoscopic endonasal route provides a good exposure, especially of the sub- and retro-chiasmatic areas, as well as of the stalk–infundibulum axis, and the third ventricle chamber. It gives better visualization, improved postoperative visual outcome for less manipulation and low complication then craniotomy. However CSF leak, DI are common known complications which have to manage promptly and appropriately.

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# Association of Serum Uric Acid with Parkinson Disease

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**Abstract:**

***Background:*** *Several studies have identified that low serum uric acid (UA) is a possible risk factor for Parkinson Disease (PD). The aim of my study was based on evaluation of association of serum uric acid with Parkinson Disease (PD).* ***Objective:*** *To evaluate the association of serum uric acid with Parkinson Disease(PD).* ***Methodology:*** *It was a case control study carried out in the Department of Neurology of Bangabandhu Sheikh Mujib Medical University. A total 50 patients of PD aged 45 years or above were taken as cases; and age and sex matched 50 healthy subjects or patients other than PD were taken as control. Serum UA levels were measured in both groups. Besides, any association was searched between serum UA with age, sex, duration and stage of PD, BMI and dietary habit.* ***Results:*** *The mean serum uric acid level in case group was 4.25±1.00 mg/dl and that of control group was 4.73±1.29 mg/dl. The mean serum uric acid in case group was statistically significant (p=0.038 which was <0.05) lower than that of control group. Serum UA levels gradually diminished as Hoehn & Yahr stage of PD increased. Also, disease duration of PD was found inversely related with serum UA. Male subjects in both case and control group had higher serum UA level than their female counter-part, but they had statistically significant higher UA in control group. In this study no correlation was found between age and BMI with serum UA in both case and control. Any association between serum UA and dietary habit was not found in this study because maximum subjects of this study used to take average protein diet.* ***Conclusion:*** *The aim of the study was to explore the association between serum uric acid with Parkinson Disease. The present study found statistically significant association between low serum uric acid with Parkinson Disease.*

***Keywords:*** *Serum uric acid (UA) and Parkinson Disease (PD).*

## Introduction:

Parkinson disease (PD) is a degenerative disease, which involves dopaminergic neuron of substantia nigra. The number of dopaminergic neuron is reduced to 30% or less in PD patient. It begins between 45 and 70 years of age with peak age of onset in the sixth decade. A tetrad of hypokinesia and bradykinesia, resting tremor, postural instability and rigidity are the core features of PD[1].

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The overall age- and gender-adjusted prevalence rate is 360 per 100,000 and incidence rate is 18 per 100,000 per year[2].

Prevalence is higher among males (19.0 per 100,000) than females (9.9 per 100,000)[3].

A diagnosis of PD can be made in patients who present with bradykinesia and at least two of the three cardinal signs- resting tremor, rigidity and postural instability. PD accounts for 75% of all cases of parkinsonism, the remaining cases result from other neurodegenerative disorder, cerebrovascular disease and drugs. Familial forms of known autosomal dominant and recessive form of PD comprise 5% of cases of PD[4].

Oxidative stress in the brain has been implicated as playing role in the onset of PD and leads to an increase in oxidative damage in the substantia nigra, manifested as lipid peroxidation, protein oxidation and DNA oxidation[5]. Such damage is probably mediated through toxic action of nitric oxide (NO) that is involved in formation of oxidizing species such as peroxynitrite and is accumulated over time possibly contributing to nigral cell death[5,6,7].

PD patients are found to have decreased antioxidant defence of cells that render them susceptible to damage from reactive oxygen species (ROS) and nitrogen species (RNOS) and others formed during cell metabolism and oxidative stress[8,9].

Uric acid is known to be an important natural antioxidant in blood and brain tissue scavenging superoxide, peroxynitrite and hydroxyl radical[7]. It has been shown to inhibit free radical-initiated lipid peroxidation and DNA damage[10]. In addition, it forms strong complexes with iron particularly ferric form[11] which may contribute to oxidative damage in PD by promoting the formation of highly reactive hydroxyl free radical[12]. Moreover, uric acid has been shown to slow dopamine (DA) auto-oxidation rate in caudate nucleus and substantia nigra homogenates of parkinsonian patients[13]. Any loss of this purine metabolite could result in a diminished free anti-oxidant capacity. The decrease level of uric acid observed in nigrostriatal human dopamine neurons[13] may contribute to an environment susceptible to oxidative stress and prevention of dopaminergic cell death in animal models of PD with the administration of UA[14]. Since DA oxidation and the consequent generation of reactive oxygen species may contribute to the degeneration of dopaminergic neurons, UA may play an important protective role.

Higher serum uric acid levels have been associated with a significantly reduced risk of PD, with evidence of a dose effect relationship implying that reduced uric acid may have a causal role in PD[15-21]. Moreover, lower plasma uric acid levels were found in treated PD patients compared to healthy controls[22].

In addition, about untreated patients with early PD, higher plasma uric acid concentrations were associated with a slower rate of clinical progression[23].

Several of these studies include only men[15,17,19]. Conflicting results concerning the association of low serum UA levels with either the risk or the progression of PD have been reported in these studies comprising both males and females[16,18,20-23]. Some report states that this correlation is significant only for men[18,21,23] whereas others did not find any gender differentiation[16,18,22].

The aim of the present study was to investigate serum uric acid levels in PD patients and control subjects; and compare with each other to find any association of serum uric acid with PD.

**Methods:**

This was a case control study. This study took place in the department of Neurology at Bangabandhu Sheikh Mujib Medical University, Dhaka which was conducted from 1st January 2010 to 31st December 2011 for the duration of two years. The target population for this study included all patients presented with Parkinson disease of age between 45 years and above; and of both sexes. Age and sex matched normal people or patients other than Parkinson disease were the controls.

A total number of 50 patients presented with Parkinson disease were enrolled in this study. Informed written consent was taken from each patient or his/ her attendant. All information regarding history, physical findings and other risk factors for PD were collected to fill the predesigned

questionnaire. Relevant physical examinations like nervous system examination, selected general and systemic examination were recorded.

**Results and Observations:**

Total 100 subjects were enrolled in this study among them 50 were PD patients comprising the case group and 50 healthy subjects on non-PD patients comprising the control group. The findings of the study are presented here.

**Table-I**

*Age distribution of the study population (n=100)*

| Age (in year) | Group I (n=50) | | Group II (n=50) | | P value |
|---|---|---|---|---|---|
| | N | % | n | % | |
| 45-50 | 16 | 32.0 | 13 | 26.0 | |
| 51-60 | 17 | 34.0 | 19 | 38.0 | |
| 61-70 | 11 | 22.0 | 16 | 32.0 | |
| >70 | 6 | 12.0 | 2 | 4.0 | |
| Mean±SD | 58.48±10.63 | | 58.36±8.91 | | $0.951^{ns}$ |
| Range (min-max) | (30-87) | | (45-80) | | |

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

Group I: Patient with Parkinson Disease (PD); Group II: Control subject.

A total of 100 subjects were included in the study. They were divided into four groups according to age. Majority of the patients were found in the age group 51-60 years, in which 17(34.0%) patients in group I and 19(38.0%) subjects in group II. The mean age was found 58.48±10.63 years in group I and 58.36 ± 8.91 years in group II. The value of unpaired t-test was 0.951 and it was not statistically significant (p>0.05).

**Table-II**

*Sex distribution of the study population (n=100)*

| Sex | Group I (n=50) | | Group II (n=50) | | P value |
|---|---|---|---|---|---|
| | N | % | n | % | |
| Male | 39 | 78.0 | 32 | 64.0 | $0.122^{ns}$ |
| Female | 11 | 22.0 | 18 | 36.0 | |

P value reached from chi square test.

Table II shows, in group I, 39 (78.0%) patients were male and 11 (22.0%) patients were female. In group II, 32 (64.0%) subjects were male and 18 (36.0%) subjects were female. There was no significant (p>0.05) difference was found between two groups regarding sex distribution. Male female ratio was 2.4:1

**Table-III**

*Distribution of mean serum uric acid level according to male and female sex of the study population (n=100)*

| | Group I (n=50) Mean±SD | Group II (n=50) Mean±SD |
|---|---|---|
| Male | 4.38±0.98 | 5.13±1.23 |
| Female | 3.77±0.94 | 4.36±1.27 |
| P value | $0.075^{ns}$ | $0.034^{s}$ |

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

In group I patients, the mean s. uric acid level was 4.38±0.98 mg/dl and 3.77±0.94 mg/dl in male and female respectively. In group II subjects the mean s. uric acid level was 5.13±1.23 mg/dl in male and 4.36±1.27 mg/dl in female. The mean s. uric acid level was higher in male subjects but not significant in group I, whereas it was significantly higher in male subjects in group II (Table III).

**Table-IV**

*Distribution of the study population according to personal history (n=100)*

| Personal history | Group I (n=50) | | Group II (n=50) | | P value |
|---|---|---|---|---|---|
| | N | % | n | % | |
| Smoking | | | | | |
| Present | 20 | 40.0 | 16 | 32.0 | $0.404^{ns}$ |
| Absent | 30 | 60.0 | 34 | 68.0 | |
| HTN | | | | | |
| Present | 15 | 30.0 | 24 | 48.0 | $0.065^{ns}$ |
| Absent | 35 | 70.0 | 26 | 52.0 | |
| Socioeconomic status* | | | | | |
| Low | 9 | 18.0 | 1 | 2.0 | |
| Middle | 40 | 80.0 | 42 | 84.0 | $0.004^{s}$ |
| High | 1 | 2.0 | 7 | 14.0 | |
| Dietary habit** | | | | | |
| Average protein diet | 44 | 88.0 | 49 | 98.0 | $0.055^{ns}$ |
| Low protein diet | 6 | 12.0 | 1 | 2.0 | |

S=Significant
NS=Not significant
P value reached from chi square test.

The above table shows the personal history of study patients. Smoking was 20(40.0%) in group I and

16(32.0%) in group II. HTN was found 15(30.0%) patients in group I and 24(48.0%) subjects in group II. Low socioeconomic status was found 9(18.0%) in group I and 1(2.0%) in group II. Middle socioeconomic status was 40(80.0%) in group I and 42(84.0%) in group II. High socioeconomic status was found 1(2.0%) in group I and 7(14.0%) in group II. In dietary habit, average protein diet was found 44(88.0%) in group I and 49(98.0%) in group II. Low protein diet was found 6(12.0%) in group I and 1 (2.0%) in group II. Only socioeconomic status was statistically significant ($p<0.05$) but others were not statistically significant ($p>0.05$) between two groups in chi square test.

*Socioeconomic status based on monthly income
Low: Tk< 15000.
Middle: Tk 15000- 40000.
High: Tk> 40000.

Reference : State of children of the world 2007, UNICEF.

**Dietary habit
Average protein diet:
65- 70%: Carbohydrate.
15- 20%: Protein.
10- 15%: Fat.

Reference: Preliminary Report on Household Income and Expenditure Survey- 2010, Bangladesh Bureau of Statistics.

**Table-V**

*Distribution of the study population according to body mass index (n=100)*

| BMI ($kg/m^2$) | Group I (n=50) | | Group II (n=50) | | P value |
|---|---|---|---|---|---|
| | N | % | n | % | |
| Under weight (<18.5) | 0 | 0.0 | 0 | 0.0 | |
| Normal weight (18.5-24.9) | 48 | 96.0 | 50 | 100.0 | |
| Over weight (25-29.9) | 2 | 4.0 | 0 | 0.0 | |
| Obesity (>30) | 0 | 0.0 | 0 | 0.0 | |
| Mean±SD Range (Min-Max) | 22.61±1.3 (20-35) | | 22.34±1.17 (19-24) | | $0.277^{ns}$ |

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

Table IV shows the mean (± SD) BMI was 22.61±1.3 $kg/m^2$ in group I and 22.34±1.17 $kg/m^2$ in group II. The mean BMI was not statistically significant ($p>0.05$) between the two groups.

**Table-VI**

*Distribution of the study population according to serum uric acid level and serum creatinine level (n=100).*

| Investigations | Group I (n=50) Mean±SD | Group II (n=50) Mean±SD | P value |
|---|---|---|---|
| Serum uric acid (mg/dl) | 4.25±1.00 | 4.73±1.29 | $0.038^{s}$ |
| Range (min-max) | (2.3-5.8) | (2.2-7.2) | |
| S. Creatinine (mg/dl) | 1.08±0.29 | 1.03±0.46 | $0.447^{ns}$ |
| Range (min-max) | (0.3-2.2) | (0.5-2.9) | |

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

Table VI shows the investigations of the study patients. The mean serum uric acid 4.25±1.00 mg/dl with range from 2.3 to 5.8 mg/dl in group I and 4.7.3±1.29 mg/dl with range 2.2 to 7.2 mg/dl in group II. The mean s. creatinine 1.08±0.29 mg/dl with range 0.3 to 2.2 mg/dl in group I and 1.03±0.46 mg/dl with range from 0.5 to 2.9 mg/dl in group II. The mean serum uric acid level was statistically significant ($p<0.05$) between the two groups but S. creatinine level was not statistically significant ($p>0.05$) between the two groups in unpaired t-test.

**Table-VII**

*Distribution of mean serum uric acid level of the study population according to dietary habit (n=100)*

| Dietary habit | Group I (n=50) Mean±SD | Group II (n=50) Mean±SD | P value |
|---|---|---|---|
| Average protein diet | 4.23±0.97 | 4.69±1.27 | $0.057^{ns}$ |
| Low protein diet | 4.35±1.3 | 7.0- | - |

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

Patients who received average protein diet, the mean s. uric acid level was 4.23±0.97 mg/dl and 4.69±1.27 mg/dl in group I and group II respectively. Patients who received low protein diet the mean s. uric acid level was 4.35±1.3 mg/dl in group I, however in group II, only one patient received low protein

diet and his s. uric acid level was 7.0 mg/dl. The mean s. uric acid level was not significant (p>0.05) in both groups in unpaired t-test.

**Table-VIII**

*Distribution of the study patients according to stages of Parkinson disease (n=100)*

| Stages of Parkinson disease | Number of patients | Percentage |
|---|---|---|
| Stage I | 26 | 52.0 |
| Stage II | 12 | 24.0 |
| Stage III | 9 | 18.0 |
| Stage IV | 1 | 2.0 |
| Stage V | 2 | 4.0 |
| Mean±SD | 1.82±1.06 | |
| Range (min-max) | (1-5) | |

Stage I: Unilateral disease

Stage II: Bilateral disease

Stage III: Bilateral disease with postural instability

Stage IV: Severe disability, patient still able to stand or walk unaided

Stage V: Wheelchair bound or bed ridden unless aided

The above table shows the stages of Parkinson disease of the study patients. The mean stages of Parkinson disease was found 1.82±1.06 with range from 1 to 5 in patients having PD.

**Table-IX**

*Distribution of mean serum uric acid level in case group (Group I) according to disease duration.*

| Serum uric acid level (mg/dl) Disease duration (in years) | Mean±SD |
|---|---|
| 1-4 | 4.27±0.95 |
| 5-8 | 4.08±0.42 |

**Table-X**

*Distribution of mean serum uric acid level in case group (Group I) according to stage of PD.*

| Stage of PD | Serum uric acid level (mg/dl) Mean ± SD |
|---|---|
| I | 4.70±0.87 |
| II | 4.19±1.02 |
| III | 3.70±1.27 |
| IV | *4.80±0.00 |
| V | 2.50± 0.14 |

*Only one patient in stage I in case group

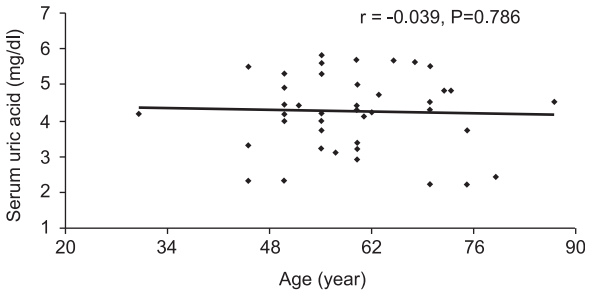


**Fig.-1:** *Scatter diagram showing no correlation (r = -0.039; p=0.786) between age with serum uric acid level (mg/dl) in patients having Parkinson disease.*

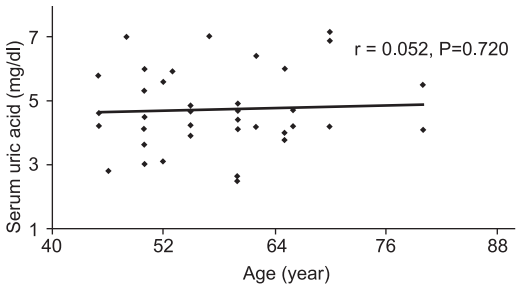


**Fig.-2:** *Scatter diagram showing no correlation (r=0.052; p=0.720) between age with serum uric acid level (mg/dl) in healthy control subject.*

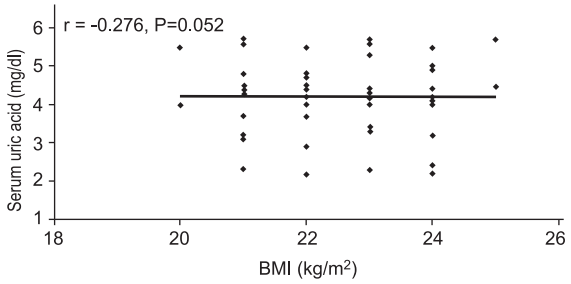


**Fig.-3:** *Scatter diagram showing no correlation (r = -0.276; p=0.052) between BMI with serum uric acid level (mg/dl) in patients having Parkinson disease.*

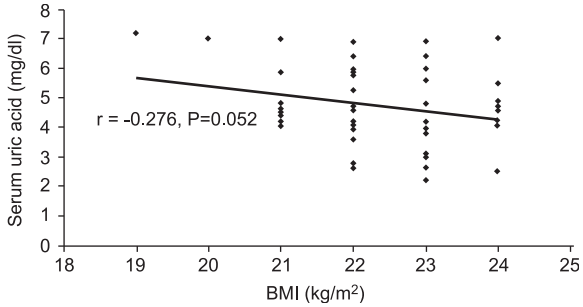


**Fig.-4:** *Scatter diagram showing no correlation (r = -0.253; p=0.076) between BMI with serum uric acid level (mg/dl) in healthy control subject.*

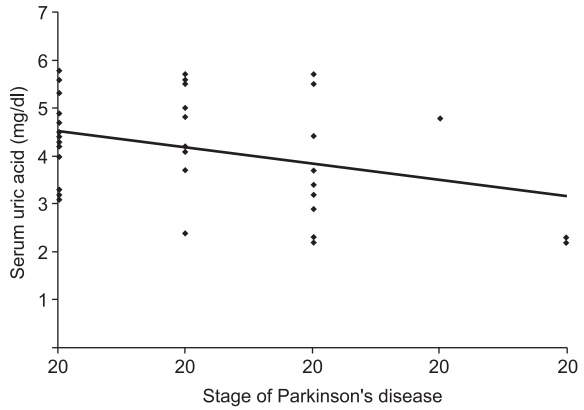


**Fig.-5:** *Scatter diagram showing significant negative correlation (r=-0.359; p=0.01) between stage of Parkinson disease with serum uric acid level (mg/dl) in patients having Parkinson disease.*

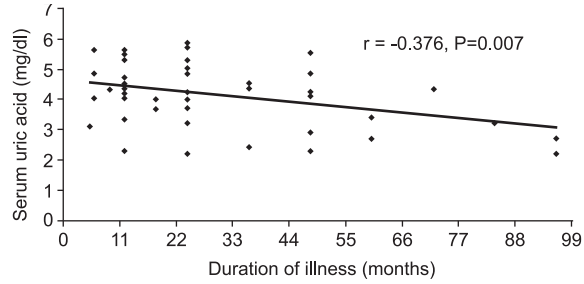


**Fig.-6:** *Scatter diagram showing significant negative correlation (r= -0.376; p=0.007) between duration of illness with serum uric acid level (mg/dl) in patients having Parkinson disease.*

**Discussion:**

This case control study was carried out with an aim to explore the association between serum uric acid level with patients of PD. For this purpose, a total 50 patients of PD age ranging from 45 years or above were purposively selected who attended in the Department of Neurology of Bangabandhu Sheikh Mujib Medical University, Dhaka and 50 healthy and non-PD subjects were taken as control during January, 2010 to December, 2011.

In the present study, patients and controls did not differ significantly from each other with respect to age. The mean age was found 58.48±10.63 years in group I (patient group) and 58.36±8.91 years in group II (control group). The value of unpaired t-test was 0.951 and it was not statistically significant (p >0.05). The results were in accordance with the study[24]. Parkinson disease usually occurs at the age of 45 years or over. In this study in group I 39 (78%) patients were male and 11 (22%) patients were female. In group II 32 (64%) subjects were male and 18 (36%) were female. There was no significant difference between two groups (p>0.05) regarding sex distribution (Table-II). These results were in accordance with the study of Andreadou et al[24].

The current study showed that serum uric acid level was 4.38±0.98 mg/dl and 3.77±0.94 mg/dl in male and female respectively in group I. In group II the mean serum uric acid level was 5.13±1.23 mg/dl in male and 4.36±1.27 mg/dl in female. The mean serum uric acid level was higher in male subjects which was not significant (p=0.075; p>0.05) in group I but it was significantly higher in male in group II (p=0.034; p<0.05). In Andreadou et al 2009 study[24] showed males had statistically significant higher serum uric acid than their female counterparts in both case and control groups. The results of the present study were also similar to that of study done by Andreadou et al.[24] except for statistically insignificant higher serum uric acid in male patients in case group. This might be due to small number of female patients in group I which might not represent actual serum uric acid level of female PD patients (Table III).

In the present study, among group I patients 20 (40%) were smoker and 30 (60%) were non-smoker. Among group II subjects, 16 (32%) were smoker and 34 (68%) were non-smoker. Smoking was not statistically significant between the two groups; (p>0.05). These results were in contradiction with that of Weisskopf study[17] which showed pack-years of smoking was associated with increasing serum uric acid concentration, indirectly suggesting decreased incidence of PD. This discrepancy might be due to increased number of female patients in control group who were non-smoker (Table IV).

About hypertension, in this study, in group I, 15 (30%) were hypertensive and 30 (60%) were non-hypertensive. In group II, 24 (48%) subjects were hypertensive and 26 (52%) were non-hypertensive. Hypertension was not statistically significant

between two groups, as p value was 0.065 which was greater than 0.05. These results were consistent with that of Weisskopf et al. study[24] which showed hypertension was not statistically associated with PD (Table- IV).

Regarding socioeconomic status, low socioeconomic status was found in 9 (18%) patients of group I and 1 (2%) in group II; middle status was found in 40 (80%) in patients in group I and 42 (84%) subjects in group II; high socioeconomic status was found in 1 (2%) in group I and 7 subjects (14%) in group II. Low socioeconomic status was significantly associated with PD on statistical point of view (p=0.004) (Table IV).

About the dietary habit, in this study, among group I patients, 44 (88%) took average protein diet and 6 (12%) took low protein diet. In group II, 49 (98%) took average protein diet and 1 patient (2%) took low protein diet. Dietary habit was not statistically significant (p>0.05) between the two groups. These results were to some extent similar to that of Gao X et al. study[19] which showed increased serving of meat per day associated with reduced occurrence of PD. (Table IV)

In the current study, in group I patients mean BMI (±SD) was 22.61±1.3 kg/m² and in group II 22.34±1.17 kg/m². The mean BMI was not statistically significant (p=0.277) between the two groups. These results were different from that of Annamaki T et al.[22] which showed mean BMI in case group was 25.1±3.4 kg/m² and in control group was 26.8±3.6 kg/m²; p value was marginally significant (p=0.05). This discordance may be because of the patient presenting in BSMMU neurology department did not represent whole of the population of PD and patients from remote and rural areas did not usually come to BSMMU. (Table V)

The present study showed that mean serum uric acid level in group I patients was 4.25±1 mg/dl and in group II subjects it was 4.73±1.29 mg/dl. Mean serum uric acid level was significantly elevated in group II on statistical point of view: p=0.038. These results (Table VII) are similar to that of several studies [24,22,19,15,17].

The mean serum creatinine in group I patients was 1.08±0.29 mg/dl and in group II subjects was 1.03±0.46 mg/dl. It was not statistically significant between the two groups (p= 0.447). It was tried deliberately so that both patient and control group to have normal renal function, thereby tried to exclude renal function as a confounding variable of serum uric acid level. (Table VI)

In the present study subjects who received average protein diet the mean serum uric acid level was 4.23±0.97 mg/dl in group I and 4.69±1.27 mg/dl in group II. Subjects who received low protein diet, the mean serum uric acid was 4.35±1.3 mg/dl in group I and only one patient in group II and his serum uric acid level was 7 mg/dl. The mean serum uric acid level was not significant between the two groups. In our country, people are used to take average protein diet. In the current study, both in case and control group, subjects who mainly took average protein diet were included, thereby it was tried to obviate the role of dietary habit over the level of serum uric acid. In the study of Garj JP et al.[25], it was shown that increase total meat intake was associated with raised level of serum uric acid. (Table VII)

In the current study there was no correlation between age of patients of group I with their serum uric acid level (r= -0.039; p= 0.786) and similarly in group II subjects (r= 0.052; p=0.720). These results were in accordance with that of Andreadou et al [24] studies where age did not affect the level of serum uric acid in both case and control groups. (Figure 1, 2)

In the study of de lau LM et al 2005[16], there was a positive association between BMI of subjects and their serum uric acid level. In the present study, there was no correlation between BMI of patients with their serum uric acid level (r= - 0.276; p= 0.052) in group I and similarly in group II (r= -0.253; p= 0.076). These results were in accordance with that of Andreadou et al[24] which showed no significant association between serum uric acid level and BMI in both patient and control groups. (Figure 3, 4)

In the present study the distribution of study patients according to stages of PD were as follows – Stage I 26 (52%), Stage II 12 (24%), Stage III 9 (18%), Stage IV 1 (2%) and Stage V 2 (4%). The serum uric acid level progressively decreased as the stage of PD increased in the present study (r= -0.359 ; p= 0.01). These results (Table VIII, Fig.-5) were similar to that of several studies[24,23].

The duration of illness had a significant negative correlation with serum uric acid level in case group in this study ( r=-0.376 ; p=o.oo7). These results were in agreement with those of some other studies[24,23] which showed increasing duration of PD were associated with progressively reduced level of serum uric acid level (r= -0.0397 ; p= 0.009 ). (Figure 6)

In the recent study of Chen et al 2009[21], the inverse association of serum UA with the risk of developing PD was significant only for men, a finding that was attributed to the small sample size. In contrast to the study of others[16,18, 20-22] did not find any gender differences regarding the risk of PD. Since low serum UA levels were found in the CSF and substantia nigra of PD patients, low serum UA level in PD patients may reflect low intracellular UA concentration in brain tissue.

UA may prevent the degradation of superoxide dismutase and consequently may assist in the removal of superoxide that reacts with nitric oxide to produce peroxynitrite and ultimately hydroxyl radical[7]. Further more it was found to be effective at preventing peroxynitrite from nitrating the tyrosine residues of protein[7,26]. Indeed an increased accumulation of 3- nitrotyrosine (a marker of peroxynitrite formation) was observed in Gord PF et al study[27]. Moreover, UA was found to undergo antioxidant reaction with DNA radicals and to induce fast chemical repair of oxidative damage on DNA that results from the toxic action of NO/ peroxynitrite[28]. In addition, it might protect cells through an astroglia mediated mechanism[29].

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***REVIEW ARTICLE***

# Role of Strength Training on Poststroke Hemiparesis, a Review on Recent Developments.

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**Abstract:**

*Stroke is the leading cause of activity limitation and participation restriction all over the world and weakness presents a more serious compromise to movement and function in poststroke hemiplegia than spasticity. In this article we have gone through publications on functional consequences of post-stroke paresis and effect of resistance training in effective stroke rehabilitation and reviewed the clinical and functional phenomena of paresis in stroke survivors, effects of high-resistance training on improvement of strength and functional capacity. By examining the various facets of weakness, we can understand the specific nature of motor impairment and can identify potential strategies to mitigate its effects, functional improvement and participation in activities. The specific aims were to emphasis the importance of strength training in the functional improvement of patients suffering from stroke with paralysis.*

***Key words:*** *stroke, strength training, functional improvement*

**Introduction:**

Stroke is a leading cause of long-term disability in the Western world, with a prevalence of approximately 900 per 100,000 persons. Because of remarkable development in the acute management of stroke, the majority of patients now survives and recovers, experiencing only a modest decrease in life expectancy [1] . In Bangladesh we do not know the actual prevalence and impact of stroke but it may approximate or exceed the statistics of the western world.

During the last decade, the number of stroke survivors has increased 30 percent worldwide. As a result considerable number of stroke survivors present with partial to complete loss of function and social burden. Though the incidence of stroke doubles with each decade beyond 60 years of age, the incidence of stroke has increased dramatically in younger individuals in the recent years [2]. This changing landscape for persons surviving stroke underscores the critical importance of providing effective rehabilitation with the potential to optimize recovery of function, minimize long-term disability, and enable functional independence so that quality of life and employment is ensured. In a poor country like Bangladesh the socioeconomic burden of disabled stroke survivors is much higher. We need to bring these young disabled into mainstream of development.

The sequel of stroke: The sequelae of stroke are multifactorial and depend heavily on the mechanism, extent, and location of the vascular lesion. The primary concern addressed in physical rehabilitation is restoration of the requisite motor function to perform the myriad of tasks encountered in daily life. These tasks range from grasping, reaching, and manipulation to more physical demanding transitional movements and complex coordinated movements, such as locomotion. Common to these motor tasks is control of muscular force, which becomes compromised with central nervous system damage and manifests as impaired intersegmental coordination, hyperreflexia or spasticity, and unilateral weakness[3].

Traditional perspectives: Spasticity presented the most significant limitation to recovery of normal motor function. Physical exertion was clinically observed to exacerbate spasticity. Therapeutic activities using forceful contractions became restricted for persons with nervous system injury. One prominent approach to treatment of adult

hemiplegia thus centered on the concept of managing muscle hypertonia. The general goal of neurorehabilitation treatment is to focus on improving control and especially the quality of movement. Meta-analyses that examined the effects of commonly used interventions for rehabilitation of both the upper and lower limb in poststroke hemiplegia reported a lack of compelling evidence that any of the existing approaches to neurorehabilitation have demonstrated superior efficacy for promoting recovery of motor function [4, 5].

Resistance training: Currently emerging evidence suggests that paresis may be directly responsible for compromised motor function [6-8]. Positive effects of resistance exercise have been demonstrated in persons with poststroke hemiplegia, and in some cases, concomitant influences on performance of functional tasks have been observed. High-intensity activities, including resistance training, could form an important component of rehabilitation programs for persons with poststroke hemiplegia.

Muscle weakness is a common impairment after stroke. However, facilitation treatment models have often emphasized the management of spasticity without addressing underlying muscle weakness. Another common intervention focus is functional training, sometimes without addressing the contributing impairments. Lower-extremity muscle strength has been correlated with gait speed in stroke patients[9]. Additionally, lower-extremity muscle strength on admission to rehabilitation is a predictor of function at discharge[10]. Lower-extremity strength has also been inversely correlated with a risk of falling in elderly individuals. The recommendation for including strengthening in the acute rehabilitation of patients with muscle weakness after stroke is based on Working Group Consensus, considering the positive relationship between muscle strength, function and prevention of falls. Researchers in strength training of post-stroke patients have studied subjects after acute rehabilitation had been completed (greater than 6 months after stroke) and demonstrated improvement in muscle strength and function with training[11, 12]. There is a lack of research on specific strength training during acute rehabilitation[13].

**Role of agonists and antagonists in functional improvement**

Weakness following stroke is referred to as either hemiparesis (mild to moderate degree of weakness) or hemiplegia (severe or complete loss of motor function) on one side of the body. However, evidence is now emerging that weakness also occurs on the ipsilesional side (traditionally termed the "nonparetic"), within a short time frame post-acute stroke[14]. In the literature, poststroke weakness has been described not only as impaired force magnitude[15], but also as a more broadly defined phenomenon, including slowness to produce force[16, 17], a rapid onset of fatigue[18], an excessive sense of effort [19], and difficulty with producing force effectively within the context of a task[20]. Throughout this review, we use the term "poststroke weakness" to include all aspects of weakness following stroke.

Co-contraction of antagonist muscles has also been found to interfere with force magnitude, rate of force production and intersegment coordination by acting as an "antagonist restraint" [21] . Significant impairment of agonist activation has been demonstrated in the paretic limb[7, 22]. Such observations lead predictably to questions of whether and how agonist activation can be improved and whether such improvement in physiologic function leads to clinically and functionally important differences in motor performance.

**Post-stroke paresis and functional impairment**

Post stroke hemiplegia is associated with significant impairments of motor function that are believed to compromise activity of daily living (ADL) performances and lead to loss of independence. However, a direct causal relationship between strength or weakness and motor function has not been established. Traditionally, a strong bias has existed against quantifying strength in hemiplegic persons. As a result, the majority of clinical research in this population has focused on outcome measures at the activity and participation levels[23]. Bohannon and Andrews observed that gait performance in 17 hemiparetic persons was significantly correlated with knee extensor torque but not with spasticity and knee extension muscle performance measured either isometrically or isokinetically correlated significantly with gait

velocity[24]. Nakamura and coworkers also observed that spasticity was unrelated to locomotors impairments[25, 26]. Isokinetic knee extension strength in the paretic limb was strongly associated with self-selected walking speed (SSWS). Lindmark and Hamrin observed a moderate relationship between SSWS and either motor scores or knee extension torque, which improved in predictive power when examined in a multivariate statistical model [27]. Pohl and coworkers observed that the combination of peak isometric knee extension force and rate of force acquisition explained a significant 12 percent of variance related to gait speed in hemi paretic adults[28]. When plantar flexion strength was added to the model, its explanatory power increased such that it became possible to predict maximal gait speed[29]. Each of the investigations just described focused on isolated muscle groups or actions. However, functional movement involves simultaneous activation and coordination of multiple muscles. This disparity may contribute in part to failure to demonstrate a direct relationship between strength and function[30].

**Strengthening Exercise Induces Neurological Recovery.**

Because poststroke weakness involves both neural and muscular changes, it seems appealing to suggest an analogy with other physiological conditions, such as aging, for which very clear benefits of strength training have been demonstrated[31]. Currently, available evidence regarding strengthening in hemiplegia indicates that significant strength gains are attainable in persons with poststroke hemiparesis at acute, subacute, and chronic stages of recovery [32, 33 34]. However, the physiological mechanisms responsible for these therapeutically induced improvements have not been demonstrated. Strengthening exercises may influence neural drive at either the supraspinal or spinal level.

**Power reaching or skilled reaching training**

Recent efforts for stroke rehabilitation have been directed toward functional and task-specific therapies that focus primarily on ADL and on grossly related precursor activities [35, 36]. A common element to these more recent approaches is substantially increased therapeutic intensity relative to traditional approaches. Increased intensity is defined by a substantially increased volume of therapeutic participation[37] an increased amount of direct participation in therapeutic activities, or performance of activities at a higher level of the subject's functional capacity[38]. Exercise dose in a stroke unit is variable and can be predicted by age and disability. Increased exercise dose is associated with improved mobility outcomes[39].

Current controversy thus centers on whether the critical variable for therapeutic efficacy is the task specificity or the intensity of effort involved in therapeutic activities. Thus, while skill-based, task-specific interventions clearly promote important use-dependent cortical reorganization, resistance training apparently can promote additional, beneficial plasticity elsewhere in the neuraxis. In all likelihood, the most effective therapeutic intervention involves a combination of elements.

**The Ultimate Goal of Rehabilitation**

The ultimate goal of rehabilitation following stroke is to promote improvements in function, activities, and participation. Collective efforts are thus required to design effective and efficient rehabilitation interventions. Weakness is not the only impairment in poststroke hemiplegia but weakness plays a significant contributory role to motor disability. By examining the various facets of weakness such as low force production, fatigability, excessive sense of effort, ineffective task-dependent force production etc. we can understand the specific nature of motor impairment and can identify potential strategies to mitigate its effects, functional improvement and participation in activities.

**Future research:**

Important area for future research is developing a greater understanding of the mechanisms underlying poststroke weakness. Without this information, we are restricted in our efforts to design appropriate rehabilitation interventions to counteract compromised function associated with poststroke weakness. Recent research evidence indicates that "task-specific" therapy[40-43] produces superior outcomes as compared to traditional therapeutic approaches[44-47]. In elders, strength training has

been demonstrated to decrease depression and improve sleep patterns, influence bone mass, decrease insulin resistance (Type II diabetes), and normalize blood pressure[48]. However, there is also evidence that increased intensity of therapy leads to more significant functional outcome. There is a need to establish the effectiveness of strength training in relation to task-specific therapies because it may be the case that strength training is an efficient means for delivering high-intensity therapy. To define and implement suitable protocols of strength training into stroke rehabilitation programs, future research should explore the specific factors such as the types of exercise, the frequency, intensity and time spent in strength training, and the number of specific exercises. Moreover, the long-term effects, both long-term training and retention of training, need to be understood. Finally, once gains in strength have been achieved we need to understand how they translate to functional gains and how they are best maintained.

Precaution: One must recognize that post stroke resistant training may not be suitable for all hemiparetic persons. In this regard, we recommend exercise should be idividualized on clinical judgment appropriate for any rehabilitation setting. High-intensity resistance training is certainly contraindicated in any case before the patient is neurologically stable. Other significant contraindications would involve postsurgical patients and persons with severe osteoporosis, acute orthopaedic or joint injuries. While the patient or client is exercising, his or her blood pressure should be monitored, and precautions should be taken to avoid conditions leading to a valsalva maneuver.

**Conclusion:**

While the number of studies is limited, emerging evidence suggests that persons with poststroke paresis can improve strength through resistance exercise in the absence of negative side effects, including exacerbation of hypertonia. Moreover, these improvements in strength appear to transfer to functional improvements. Despite increases in strength, improvements in functional performance may not occur in hemiplegic persons with low strength and low performance. It is entirely possible that vigorous strength training promotes positive effects on other aspects of physiologic function in this type of at-risk population. Still, many unresolved issues remain. The potential for strength training to improve the overall outcomes of rehabilitation for persons with poststroke hemiplegia warrants further investigation.

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## CASE REPORTS

# Tolosa-Hunt Syndrome: A Case Report and Review of the Literature

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**Abstract:**

*Tolosa-Hunt Syndrome is a painful ophthalmoplegia which is characterized by periorbital or hemicranial pain, with ipsilateral ocular motor nerve palsies, oculosympathetic paralysis, sensory loss in the distribution of the ophthalmic and occasionally the maxillary division of the trigeminal nerve. Various combinations of these cranial nerve palsies may occur, localising the pathological process to the region of the cavernous sinus/superior orbital fissure. We report the case of a patient presented with severe pain in the right side of face which was periorbital with ipsilateral 3rd,4th, 6th cranial nerve palsies along with ophthalmic and maxillary division of trigeminal nerve involvement. MRI of orbit showed hypo-intense lesion in right cavernous sinus extending to right superior orbital fissure (suggestive of granulomatous infiltration). After taking oral steroid her pain was relieved quickly and cranial nerve palsies reversed within one week. Azathioprin was added and she was completely cured of within next three months.*

**Introduction:**

Tolosa-Hunt Syndrome is caused by a non specific inflammatory process with occasional granulomatous features in the region of superior orbital fissure often extending into the cavernous sinus. It was first described by Tolosa in 1954[1] and by Hunt in 1961. It is a rare disorder characterized by painful ophthalmoplegia[2] with palsies of third, fourth ,sixth cranial nerves as well as first and second division of trigeminal nerve. In 2004, the International Headache Society included granuloma as one of its diagnostic criteria and now is a part of classification ICHD – II. ICD-10 for Tolosa Hunt Syndrome is G44.850[3]. With no sex predilection Tolosa-Hunt syndrome can affect people of any age from 1st to 8th decades of life. The characteristic findings are pain which may precede the ophthalmoplegia by several days, or may not appear until sometime later. Pain is steady, felt behind the eye often described as “gnawing” or “boring”. The neurological involvement is not confined to the third cranial nerve, but may include the fourth, sixth, and first division of the fifth cranial nerves. Periarterial sympathetic fibers and the optic nerve may also be involved. Symptoms last for days to weeks. Spontaneous remissions may occur and sometimes with residual neurological deficit. Attacks recur at intervals of months or years. Exhaustive studies, including angiography and surgical exploration have produced no evidence of involvement of structures outside of the cavernous sinus. There is no systemic reaction[4].

The etiology of Tolosa-Hunt syndrome remains unknown. A possible risk factor for Tolosa-Hunt syndrome is a recent viral infection. It seems that the syndrome falls within the range of idiopathic, sterile inflammation of the cavernous sinus. Its pathology is described as fibroblastic, lymphocytic, and plasmacytic infiltration of the cavernous sinus. Pathology may extend to involve the superior orbital fissure (sphenocavernous or parasellar syndrome)[5] or orbital apex and affect the nerve. Hunt et al [2]

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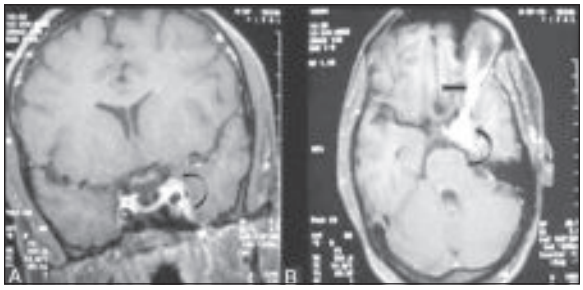
corroborated these findings,emphasizing the lack of necrosis and pointed out that "such inflammatory changes, in a tight connective tissue, may exert pressure upon the penetrating nerves". Subsequent reports have shown granulomatous inflammation, with epithelioid cells and occasional giant cells[6,7]. Necrosis may also be seen and no infectious organism was found.

MRI of brain may show evidence of inflammatory changes in the region of the anterior cavernous sinus, superior orbital fissure and/ or orbital apex[8] and signal changes shows:

- T1 : involved region is iso intense [9] to hyper intense[8] compared with muscle
- T2 : involved region is hyper intense
- C+ (Gd) : may show contrast enhancement during active phase with resolution of enhancement following treatment [10,11]

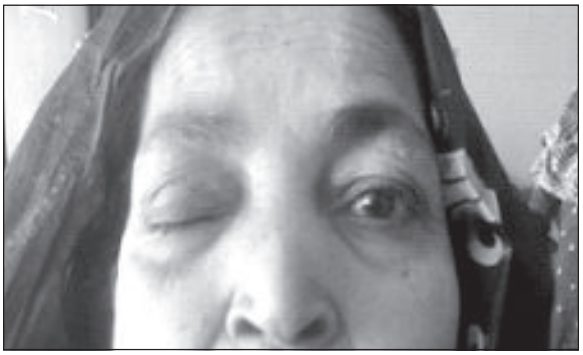


In fact, during the initial patient evaluation there are often no clues in the history or physical examination to distinguish Tolosa-Hunt syndrome from other causes of painful ophthalmoplegia. Therefore, the clinician should be aware of causes of parasellar syndrome and other entities producing painful ophthalmoplegia. To establish the diagnosis biopsy is required through neurosurgical approach which is rarely done[12-16.]

Tolosa-Hunt syndrome is not a fatal disorder, and can be treated with steroid.[2] This usually provides pain relief within 24-72 hours of starting the medication. The visual problems and numbness in frontal region may take weeks or months to resolve, and sometimes the symptoms never go away completely. It is clear that spontaneous remissions may occur, but there is no doubt that corticosteroids markedly reduce the periorbital pain. Although steroids are generally tapered over weeks to months, in some cases prolonged therapy may be necessary. Because of this fundamental limitation of initial imaging studies, some authorities would suggest that resolution of imaging abnormalities after a course of systemic corticosteroids should be considered "diagnostic" of Tolosa-Hunt syndrome[17,18] .As many as 30-40% of individuals may have a relapse of Tolosa-Hunt syndrome, usually on the same side.

**Case report:**

Our patient was a 70 yrs old lady who presented with a 3 weeks history of severe periocular headache which was sudden in onset, global, continuous, associated with vomiting for 2 times, this relieved the headache to some extent. The following morning when she woke up from sleep, found that she cannot open her right eye voluntarily but can do manually. Her left eye was normal as well as vision. Headache and right periorbital pain was present. She never had this kind of problem before.



On clinical examination, her vital signs were normal. She had complete ptosis on right sided, total paralysis of right extraocular muscles indicating right third, fourth, sixth nerve palsy. Pupil was dilated, non-reacting to light on right side. sensory loss of right sided ophthalmic and maxillary distribution over face. Fundoscopic examination was normal. Left eye findings were normal and no other neurological deficit was found. Routine blood tests and cerebral fluid study were within normal limit. Erythrocyte sedimentation rate (ESR) was significantly increased but ANA, p-ANCA, c-ANCA was within normal limit. An MRI was done before admission which was inconclusive. Magnetic resonance angiography

(MRA) and magnetic resonance venography (MRV) was done where MRA was normal and MRV showed non-visualization of left transverse sinus which could not be correlated with clinical findings. No evidence of cavernous sinus or superior ophthalmic vein (SOV) thrombosis was seen. Repeat MRI of orbit and cavernous sinus with contrast was done in multiple axial, coronal and sagittal sections which showed iso to hypo-intense lesion in right cavernous sinus extending upto right superior orbital fissure and left cavernous sinus also. The lesion was brilliantly contrast enhancing and causing significant compression of the neurovascular structure of right cavernous sinus. Both optic nerves were spared.ICA was also normal in diameter.

Patient was treated with oral steroid 1mg/kg body weight which started 3 weeks after onset of her illness. She got relief from headache and periorbital pain within 3 days but improvement of third, fourth, sixth or second division of trigeminal nerve palsy except ophthalmic division was noted after one week. Then oral Azathioprin was added. Patient was discharged from hospital and followed up in every fortnightly for next three months. She was completely cured of her ailments after three months.

**Discussion:**

Tolosa[1] first described the condition in 1954, in a patient with unilateral recurrent painful ophthalmoplegia involving cranial nerves III, IV, VI and V1. The patient was imaged using carotid angiography and segmental narrowing of the carotid siphon was seen. Hunt *et al*. described 6 patients with similar clinical findings in 1961, and proposed a low-grade non-specific inflammation of the cavernous sinus and its walls as the cause of the syndrome[2]. Pathologically, infiltration of lymphocytes and plasma cells as well as thickening of the dura mater was seen. In 1966 Smith and Taxdal termed this condition as Tolosa-Hunt syndrome[18]. The latter author stressed the importance of the dramatic rapid response to steroid therapy. Neuro-imaging, particularly MRI, is an essential part of the workup of any patient presenting with features of THS, as these features are non-specific and have a wide differential diagnosis, including meningioma, sarcoidosis, pituitary tumours, tuberculous meningitis (TBM) and lymphoma[19]. MRI findings classically demonstrate a soft-tissue mass lesion involving the superior orbital fissure or cavernous sinus. Signal characteristics are typically hypo intense to fat and isointense to muscle on short TR/TE sequences and isointense to fat on long TR/TE sequences[20]. Significant enhancement of the mass lesion is demonstrated on CE sequences. Of particular value is the post-contrast fat-saturated thin-slice coronal image through the orbital apex and cavernous sinus. THS essentially remains a diagnosis of exclusion. The role of the radiologist is to exclude other conditions causing similar clinical features. Some authors reported that using carotid angiography there was segmental narrowing of the carotid siphon was seen[21]. Distinctive MRI findings and rapid resolution of clinical symptoms with steroid therapy are characteristic. So,Tolosa Hunt syndrome is diagnosed by exclusion and which should be done by clinical and MRI finding and treatment response to steroid therapy which was very much characteristic to this case.

**Conclusion:**

Tolosa-Hunt syndrome is a rare disorder and the pathogenetic basis remains unknown, and on clinical stand point it can be regarded as a distinct entity which may be simulated by various other disorders. Tolosa-Hunt syndrome is not a fatal disorder, and can be treated with steroid medication such as prednisone. Though treatment response is good, relapse may occur. Hence careful evaluation, appropriate treatment, and scrupulous follow up are required. Because many disorders can have similar symptoms, individuals should report any new symptoms or side effects from treatment to their physicians.

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# A Young Male with Typical Presentation of Amyotrophic Lateral Sclerosis (ALS)

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**Abstract:**

*Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular condition characterized by proximal and distal muscle wasting, weakness, fasciculation. The etiology of the disease is unknown. The annual incidence rate is one to two cases per 100,000 persons. The disease is most commonly presents in middle age, mostly after the age of 50 and very uncommon before the age of 30 years and affects men more than women. Usually it present with limb muscle weakness, cramps, occasionally fasciculations and sometimes with dysarthria, dysphagia. Symptoms often begin focally in one part and spread gradually but relentlessly to become widespread. Over a period of months or years, patients with ALS develop severe, progressive muscular weakness and other symptoms caused by loss of function in both upper and lower motor neurons. Sphincter control, sensory function, intellectual abilities and skin integrity are preserved. Patients become completely disabled, often requiring ventilatory support and gastrostomy. Death usually occurs within five years of diagnosis and is attributed to respiratory failure or cachexia. Current management involves aggressive, individualized alleviation of symptoms and complications. We are reporting an 18 year old right handed male presented with typical features of ALS . The purpose for reporting was for its rarity before 40 years and that had a typical clinical features of young-adult ALS, and to compare them with features of the common adult-onset type.*

**Introduction:**

Amyotrophic lateral sclerosis (ALS) was first described in 1869 by the French neurologist Jean-Martin Charcot. It became familial after the popular baseball player Lou Gehrig was diagnosed with the disease in 1939 and best known as Lou Gehrig's disease[1].It is a fatal neuro degenerative disease characterized by progressive muscular weakness reflecting degeneration of motor neurons in the motor cortex, brainstem and spinal cord[2,3]. It leads to muscle weakness and wasting due to unsent messages to muscles. The cause of ALS is unknown, although 5-10% of cases are familial.

The age of onset is usually after the age of 50 and very uncommon before the age of 30. Juvenile 'ALS' refers to those with symptoms onset consistently before age 25 years, typically in association with a positive family history and slow progression[5].Three genotypes of juvenile ALS have now been described. ALS2 (infantile ascending hereditary spastic paraparesis)[6] shows autosomal recessive inheritance with very slow progression associated with a loss of function of the gene alsin and to date nine different mutations have been identified[7]. There is early onset of limb and facial muscle weakness accompanied by bulbar or pseudobulbar symptoms and upper motor neuron features predominate. ALS is associated with mutations in SETX[8] and also known as distal hereditary motor neuronopathy with pyramidal features, shows autosomal dominant inheritance.

ALS is linked to chromosome 15 which is characterized by onset in the first or second decade of life with slowly progressive weakness and atrophy

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of the hands and feet and only later bulbar muscles[5-9]. Upper motor neuron features are a late development[10]. 'Young-onset' Amyotrophic Lateral Sclerosis is considered to be similar to 'classic' ALS with mixed upper and lower motor neuron features commencing before an arbitrary cut-off age of 45 years and apparently sporadic. There is potential overlap of young onset with juvenile ALS in terms of age of onset, but cases of classical ALS with onset 20 years are exceptional[11] and may indicate a different condition.

Males are more commonly affected than females[12].The incidence is about 1-2 per 100,000[13]. ALS affects motor neurons at 2 or more levels supplying multiple regions of the body. It affects lower motor neurons that reside in the anterior horn of the spinal cord and in the brain stem; corticospinal upper motor neurons that reside in the pre-central gyrus and pre-frontal motor neurons that are involved in planning or orchestrating the work of the upper and lower motor neuron. Loss of lower motor neurons leads to progressive muscle weakness and wasting (atrophy). Loss of corticospinal upper motor neurons may produce spasticity and abnormally active reflexes.

The term classic amyotrophic lateral sclerosis is reserved for the form of disease that involves both upper and lower motor neurons. The classic form of sporadic ALS usually starts as dysfunction or weakness in one part of the body and spreads gradually within that part and then to the rest of the body. If only lower motor neurons are involved, the disease is called progressive muscular atrophy (PMA). When only upper motor neurons are involved, the disease is called Primary lateral sclerosis (PLS). Rarely, the disease is restricted to bulbar muscles, in which case it is called progressive bulbar palsy (PBP). In most patients who present with initial involvement of bulbar muscles, the disease evolves to classic ALS.

Worldwide, ALS occurs sporadically in 90-95% of cases and with Mendelian patterns of heredity (familial ALS) in 5-10% of cases. Most familial ALS is inherited in an autosomal dominant pattern[14].

The diagnosis of ALS is primarily clinical. Electro-diagnostic testing contributes to the diagnostic accuracy. It is relentlessly progressive; the mean time from diagnosis to death is 1 year, with most patients dying within 3-5 years of the onset of symptoms. Younger patients and those with early bulbar symptoms tend to show a more rapid course. Death is usually from respiratory failure, infection and the complications of immobility. Prognosis is better for progressive lateral sclerosis and progressive muscular atrophy. Here, we report a case of an amyotrophic lateral sclerosis of 18 years old man as because it is very uncommon before the age of 30 years.

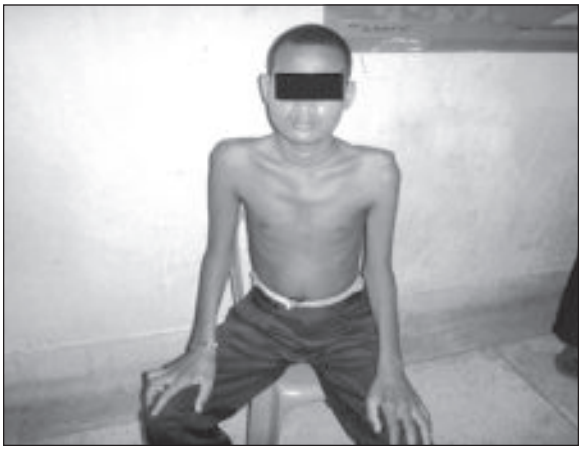

**Fig.-1:** *The Patient with generalized muscle wasting*

**Case history:**

A 18 years old male, normotensive, non-diabetic college student hailing from Rangpur, Bangladesh admitted in Rangpur Medical College hospital, Rangpur, Bangladesh presented with progressive weakness and wasting of all four limbs for six months and slurring of speech for three months. Weakness first appeared in lower limbs and then gradually involved the upper limbs over three months associated with progressive muscle wasting. Weakness and wasting was bilaterally symmetrical involved both proximal and distal part of all four limbs equally. Patient also gave history of muscle twitching in different part of his body. He complained slurring of speech for last three months which also gradually increased associated with dysphonia and nasal regurgitation of liquid but no complain of numbness, tingling sensation or paresthesia in any part of his body. There was no history of fever, headache,

unconsciousness or trauma to the head and neck. His bowel and bladder habit is normal. No member of his family suffered from such type of illness and no history of parental consanguinity.

General physical examination was unremarkable except the patient was emaciated. On neurological examination higher mental function was normal except speech which was slurred. Regarding cranial nerves examination- jaw jerk was present, palatal movement was diminished bilaterally and gag reflex was absent. Wasting with fasciculation of tongue observed but other cranial nerves were intact. There was symmetrical wasting of muscles of all four limbs but distal wasting was more than proximal. Wide spread fasciculations were observed in both calves, quadriceps, hamstring, gluteal muscles of lower limbs and biceps, triceps, deltoids, pectoralis, supraspinatus muscles of upper limbs. Tone slightly increased in both lower limbs but reduced in both upper limbs. Muscle power was 3/5 in both upper limbs and 2/5 in both lower limbs. Biceps, triceps and supinator jerks of both upper limbs were exaggerated but knee and ankle jerks of both lower limbs were diminished. Plantar response was extensor bilaterally. Co-ordination and gait was impaired. Sensory system found intact. Signs of meningeal irritation were absent. The laboratory investigations reports are summarized below-

TC of WBC 8, 500/$mm^3$, DC of WBC N-76%, L-15%, M-3%, E-4%; Hb%- 12.3 gm/dL, Platelet count- 3.5 lacs/$mm^3$, ESR- 34 mm in the 1$^{st}$ hour; RBS 6.6 mmol/L; S creatinine 0.7 mg/dl; S. bilirubin 0.7 mg/dl, AST 47 U/L, ALT 26 U/L, Alkaline phosphatase 99 U/L; S. electrolyte $Na^+$ 142 mmol/L, $K^+$ 3.9 mmol/L; Fasting lipid profile- Cholesterol 176 mg/dl, TG 281 mg/dl, HDL 44 mg/dl and LDL 93 mg/dl; $FT_4$ 1.18ng/dl, TSH 2.17 IU/ ml; VDRL non-reative; HBsAg (-)ve; ANA (-)ve; serum Vit $B_{12}$ level 631 pgm/ml, serum Folic acid level 3.99 pgm/ml; MRI of cervical spine and brain reveals normal study; EMG showed diffuse neurogenic degeneration in the form of active denervation of bulbar and thoracic myotomes and active denervation with chronic reinnervation of cervical and lumbosacral myotomes.

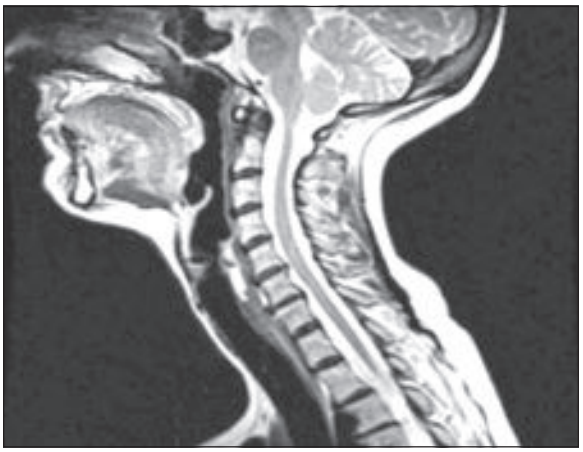

**Fig.-2:** *MRI of Cervical spine of the patient showing normal anatomy.*

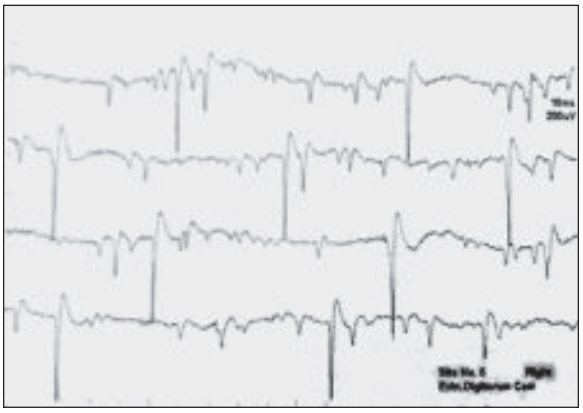

**Fig.-3:** *EMG tracing of the patient*

**Discussion:**

Amyotrophic lateral sclerosis (ALS) is a progressive and devastating neuro-degenerative disorder that affects motor neurons. It is the most common type of motor neuron disorder and does not lend itself to a quick definitive diagnosis early in its presentation. Often, neurologists need many months to exclude all other possible diagnoses in a patient presenting with upper and lower motor neuron signs. The characteristic form of this disease features the simultaneous presence of both upper motor neuron (UMN) and lower motor neuron (LMN) lesion signs, with progression from one region of the neuraxis to the next. Many cases of ALS will begin with the LMN form and then with time progress to show UMN involvement. Most ALS is sporadic and men tend to develop ALS more often than women with a male/

female ratio of about 2:1[15]. Death, usually from respiratory compromise, occurs approximately three years after onset of symptoms[16].Because of the near-uniform 'kiss of death' implications that a diagnosis of ALS carries, all efforts must be sought to exclude alternative diagnoses. In addition to electro-diagnostic studies, investigations usually include neuro-imaging studies to exclude anatomic structural processes such as cervical myelopathies and typical laboratory investigations to search for any potential treatable metabolic abnormality. Nerve conduction studies and needle electromyography are useful for confirming the diagnosis of ALS and for excluding peripheral conditions that resemble ALS. Laboratory test results generally are normal and are performed primarily to rule out other disease processes. The most common laboratory tests done are for serum vitamin B12 levels (to rule out sub-acute combined degeneration), parathyroid hormone levels (to rule out hyperparathyroidism) and serum protein electrophoresis with immune-fixation (to rule out multiple myeloma or MGUS). Imaging studies need to be tailored to the clinical presentation. Neuro-imaging may include computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain and spinal cord. These studies may be helpful to rule out structural lesions or neurological conditions that may mimic ALS. Examination of cerebrospinal fluid usually is not necessary. Genetic testing may be performed to identify gene defects in some familial types of ALS as well as other inherited motor neuron diseases[17].

Our patient is a sporadic case. The patient typically presented with weakness and wasting of all four limbs and slurring of speech but no bowel and bladder involvement. On physical examination, he was found emaciated. On neurological examination, speech was found slurred, bulk of the muscles of all four limbs were reduced, tone was increased in both upper limbs but reduced in both lower limbs, muscle power were 3/5 in upper limbs and 2/5 in lower limbs, deep tendon reflexes were absent in both upper limbs and exaggerated in both lower limbs, plantar responses were extensor bilaterally. Sensory system was found intact & signs of meningeal irritations were absent .The diagnosis of ALS is clinical, based on the characteristic signs of progressive weakness, atrophy, fasciculations and hyperreflexia affecting several regions of the body. So, our patient's all clinical features are consistent with ALS. To establish the diagnosis of ALS beside the consistent clinical features one must have to exclude the probable differential diagnosis.EMG of the patient showed diffuse neurogenic degeneration in the form of active denervation of bulbar, cervical, thoracic and lumbosacral myotomes. The differential diagnosis may include musculoskeletal, neurologic or systemic conditions. Here we have excluded some possible differential diagnosis by laboratory investigations and imaging like Spinal cord lesions(tumors, syringomyelia, vascular malformations), Spinal bone lesions (spondylosis, cervical rib, metastatic tumors), infections (syphilis), Vitamin $B_{12}$ deficiency, endocrine disorder (hyperthyroidism, hyperparathyroidism, DM) and connective tissue disease (SLE).Genetic testing may be performed to identify gene defects in ALS but it is not available here.

The management of ALS is a complex and demanding team effort requiring individualized therapy and continual adaptation of medications and therapies. The only agent currently labeled for the treatment of ALS is riluzole which believed to decrease glutamate release. One large study reported that 56.8 percent of patients treated with 100 mg of riluzole daily were alive without tracheostomy after 18 months, compared with 50.4 percent of patients who received a placebo, a clinically small but statistically significant difference[18]. But no study has reported that the drug halts the disease process[19]. Adverse effects include asthenia, nausea, dizziness, elevation of liver enzymes and granulocytopenia[20].

We have prescribed riluzole 50 mg 12 hourly to our patient. Patient and his family was properly educated and counseled about the disease. The patient referred to the department of Physical Medicine and Rehabilitation of Rangpur Medical College and Hospital, Rangpur, Bangladesh, for proper physiotherapeutic management. We discharged him on request and advised to continue physiotherapy and follow up.

**Conclusion:**

ALS is a fatal disease, with median survival of 3-5 years. Our findings showed that ALS can occur in younger age group and predominantly upper limb involvement. As this group represent a distinctive clinical variant, it needs to evaluate phenotypically, which was not done in this case due lack of facility of this test. Although ALS is incurable, the management involves aggressive, individualized alleviation of symptoms and complications that can prolong meaningful quality of life; therefore, diagnosis is important for patient and families.

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