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ORIGINAL ARTICLE

Determination of number of Extracranial and Intracranial Atherosclerotic Arterial Stenosis in Patients of Ischemic Stroke with Diabetes Mellitus under DSA Evaluation

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Abstract:

Objective: *To evaluate the solitary & multiple site of extracranial and intracranial atherosclerotic arterial stenosis in patients of ischemic stroke with diabetes mellitus.*

Methodology: *This retrospective observational study was conducted among the patients having ischemic stroke with diabetes mellitus who were admitted in Dhaka Medical College & Hospital (DMCH) out patient department during March 2010 to February 2011. A total of 30 patients with ischemic stroke and diabetes mellitus were included in the study. CT scan of brain was done to every patient to confirm the diagnosis. Digital subtraction angiography was performed for complete evaluation.*

Result: *The mean (±SD) age was 57.9±9.2 years with a range from 43 to 80 years and male female ratio was 29:1. Among 21 patients with extracranial stenosis, either single, double and triple or more lesions were found in 53.3%, 85.7% and 87.5% of patients respectively. Again among 9 patients with intracranial stenosis, it was observed that 46.7% of patients had single lesion stenosis, 14.3% of patient had double lesion stenosis and 12.5% of patients had triple or more lesion stenosis. Double (85.7%) and triple (87.5%) lesions were significantly ($p<0.05$) higher in extracranial stenosis compared to intracranial stenosis (14.3% and 12.5% respectively). Most (78.9%) of the patients had >70% stenosis in extracranial arteries and 21.1% in intracranial arteries. Patients with >70% stenosis were significantly ($p<0.05$) higher in extracranial arteries.*

Conclusion: *A conclusion can be made from the above mentioned result that occurrence of multiple site of lesions and more severe stenosis occurred more in extracranial group than in intracranial group of ischemic stroke patients among diabetic population of Bangladesh.*

Introduction:

Stroke is a medical emergency and can cause permanent neurological damage, even death. It is the leading cause of adult disability in the United States and Europe and second cause of death worldwide[1]. The incidence and mortality rate due

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to stroke is higher in Asians than that in Whites. Risk factors for stroke includes diabetes mellitus, advanced age, hypertension, previous stroke or transient ischaemic attack (TIA), high cholesterol, cigarette smoking and atrial fibrillation[2,3].

An ischemic stroke typically results from blockage of an artery that supplies the brain, most commonly a branch of one of the internal carotid arteries. Commonly, blockages are blood clots (thrombi) or pieces of fatty deposits (atheromas or plaques) due to atherosclerosis[4].The pathological changes associated with atherosclerosis are several-fold more frequent in person with diabetes. In diabetic people, atheromatous lesions occur earlier in life and are more extensive and severe[5]. It is now well established that atherosclerotic disease (atheroma) is a strong and independent risk factor for ischemic stroke. The thickness of the atheroma and its morphology (protruding, ulcerated, calcified or mobile plaque) are both strongly related to increased risk of ischemic stroke. Plaques >4 mm thick are presumed to be of very high risk. Thus, the burden of atherosclerotic disease has been directly implicated in the increased risk for ischemic stroke. Intracranial carotid lesions are reported to be more common than extracranial carotid lesions among Japanese, Korean, Chinese and African-American as documented by angiographic and autopsy studies in stroke patients, which is in sharp contrast to the pattern of cerebral atherosclerosis in whites[6-8].

This study was aimed to evaluate distribution of intracranial and extracranial atherosclerotic arterial stenosis in patients of ischemic stroke with diabetes mellitus by digital subtraction angiography (DSA) though it is invasive, relatively costly and uses radio contrast dye. This will also evaluate the relationship of diabetes mellitus with intracranial and extracranial atherosclerotic arterial stenosis in ischemic stroke patients. This study will help the patient of ischemic stroke with diabetes mellitus among Bangladeshi population regarding their etiological evaluation with management.

Methodology :

Study Design : Retrospective cross-sectional observational study.

Place of Study : Department of Neurology, Dhaka Medical College Hospital (DMCH), Dhaka.

Duration of Study : March 2010 to February 2011.

Sample Size : Sample size was 30. Patients of ischemic stroke with diabetes mellitus were included.

Sampling Procedure : Non- random and purposive.

Inclusion Criteria : Patients of ischemic stroke with diabetes mellitus who were clinically suggestive and confirmed by CT scan of Brain and patients having stenosis of >50% stenosis were considered significant and were included in this study. Other inclsion criteria were investigations (e.g. Protein C, Protein S, Antithrombin III, Transthoracic and Transoesophageal Echocardiogram), which were within normal limit and adult patients with age more than 40 years of both gender.

Exclusion Criteria: Hemorrhagic stroke, non-diabetic patients, mixed type stenosis (both extracranial and intracranial stenosis) evaluated by DSA and patients who did not give consent to take part in the study.

Analysis of data : Statistical analysis was performed using SPSS 16.0 programme. Data was defined as mean (±standard deviation), frequency distribution and percentage. Z test was used for proportion test. P values <0.05 was considered to be statistically significant.

Results :

The mean (±SD) age was 57.9±9.2 years with range from 43 to 80 years(Table-I) and male female ratio was 29:1. Among 21 patients with extracranial stenosis, single, double and triple or more lesions were found in 8 (53.3%) ,6 (85.7%) and 7 (87.5%) patients respectively(Table II). On the other hand, among 9 patients with intracranial stenosis, it was observed that 7 patients (46.7%) had single lesion stenosis, 1 patient (14.3%) had double lesion stenosis and 1 patient (12.5%) had triple or more lesion stenosis. Double and triple lesions were significantly ($p<0.05$) higher in extracranial stenosis in comparison to intracranial stenosis. Moreover 15 patients (78.9%) had >70% stenosis in extracranial arteries and 4 patients (21.1%) had >70% stenosis in intracranial arteries. 51% to 70% of stenosis was found in 6 (54.5%) patients in extracranial sites and in 5 (21.1%) patients in intracranial sites. Patients with >70% stenosis were significantly ($p<0.05$) higher in extracranial arteries(Table III).

Table-I

Distribution of the respondents' age by group (n=30)

Age (in years)	Number of patients(n=30)	Percentage
41 – 50	8	26.7
51 – 60	11	36.7
61 – 70	10	33.3
71 – 80	1	3.3
Mean±SD	57.9	±9.2
Range (Mean-Max)	(43	-80)

Table-II

Distribution of the respondents' according to the number of lesions (n=30)

Number of Lesions	Extracranial Stenosis(n=21)		Intracranial Stenosis(n=9)		Z value	P value
	N	%	n	%		
Single	8	53.3	7	46.7	0.36	0.054^{ns}
Double	6	85.7	1	14.3	5.58	0.001^{s}
Triple or more	7	87.5	1	12.5	6.21	0.001^{s}

Table-III

Distribution of the respondents' according to the significant (i.e. >50%) degree of stenosis (n=30)

Percentage of stenosis	Extracranial Stenosis(n=21)		Intracranial Stenosis(n=9)		Z value	P value
	N	%	N	%		
51 – 70	6	54.5	5	45.5	0.42	>0.05^{ns}
>70	15	78.9	4	21.1	4.37	0.001^{s}

Discussion:

This retrospective observational study was carried out with an aim to evaluate the solitary & multiple site of extracranial and intracranial atherosclerotic arterial stenosis by digital subtraction angiography in 30 patients of ischemic stroke with diabetes mellitus who attended in the out-patient department of Neurology, Dhaka Medical College Hospital (DMCH) during the period of March 2010 to February 2011.

Risk factors more commonly observed were IHD, dyslipidaemia, H/O TIA, hypertension, obesity and smoking. A study in Hong Kong China observed similar risk factors including hypertension (71.0%), smoking (38.7%), previous H/O stroke (51.6%) and IHD (19.4%)[9].Another study reported hypertension and diabetes mellitus as risk factors associated only with intracranial atherosclerosis ($p<0.001$), whereas ischemic heart disease was associated with atherosclerosis in both the intracranial and extracranial ($p=0.012$) vessels ($p<0.001$)[10]. Smoking was associated with narrowing of the extracranial vessels only ($p=0.001$). A study on Korean patients showed diabetes mellitus as only significant factor associated with combined intracranial atherosclerosis and extracranial carotid artery disease[8]. These findings are comparable with the present study regarding the risk factors.

Regarding 2 hours after breakfast blood sugar, most of the 26 patients (86.7%) had blood sugar level between 7.8 to 20 mmol/L, 3 patients (10.0%) had >20 mmol/L and only 1 patient (3.3%) had normal (<7.7 mmol/L) and regarding level of HbA_{1C} (Glycated Haemoglobin), a higher portion of 18 patients (60.0%) had >7% followed by 11 patients (36.7%) had 6.5% to 7% and only 1 patient (3.3%) had normal level. That is most of the patients had uncontrolled diabetes mellitus in this study. Data from the Northern Manhattan Stroke study reported that patients with intracranial atherosclerosis had a higher prevalence of diabetes (67%) when compared to those with extracranial atherosclerosis or non-atherosclerotic (60% and 48% respectively)[11].

In this study, single lesions were found among 53.3% and 46.7% in extracranial stenosis and intracranial stenosis respectively. Double (85.7%) and triple (87.5%) lesions were significantly ($p<0.05$) higher in extracranial stenosis with compared to intracranial stenosis (14.3% and 12.5% respectively). Similarly two separate studies showed that single-stenosis was more common in intracranial stenosis and multiple stenoses were significantly higher in extracranial stenosis[8,12].

Regarding the degree arterial diameter of stenosis it was observed that, >70% stenosis had in extracranial sites in most (78.9%) of the patients and 21.1% of patients in intracranial sites. 51% to 70% of stenosis was found in 54.5% of patients in extracranial sites and 21.1% of patients in intracranial sites. Patients with >70% stenosis was significantly ($p<0.05$) higher in extracranial stenosis. Similar findings were observed in a study on 'Pattern of atherosclerotic carotid stenosis in Korean patients with stroke' that severe stenosis was in extracranial stenosis[12].

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Efficacy, Safety and tolerability of the once-daily 10 cm² rivastigmine patch formulation in the patients with dementia (with probable Alzheimer's disease)

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Abstract

Back ground: *Treatment compliance in patients with Alzheimer's disease is particularly important as patients receiving regular treatment have a greater chance of slowing or delaying disease progression. Transdermal delivery has the potential for providing continuous drug delivery and steady plasma levels. Current study aimed to evaluate safety and tolerability of rivastigmine patch, to assess patient compliance and to assess the efficacy of treatment in patients with dementia (with probable Alzheimer's disease).* ***Methods:*** *A total of 112 dementia patients (with a diagnosis of probable Alzheimer's disease) from 12 centers were enrolled who were residing with someone in the communities throughout the study. After eligibility, and baseline assessments, patients were entered a 24-week open label treatment phase. All patients were started with application of one 5 cm² patch, followed by an up-titration to the target dose of 10 cm² patch size. Efficacy assessments were performed at weeks 12 and 24 in terms of MMSE and GDS score. Safety was monitored at all assessment points based mainly on the frequency of adverse events.* ***Results:*** *Analysis of baseline and available data until the drop out revealed no significant differentials. Around 95% of the study participants could receive 10 cm² patch size, showing a very high tolerability of the patch. Concurrent medication use also showed significant reduction to 16.3% patient in the end from 25% at baseline. The average MMSE score increased to 19.3 (±3.1) at 12th week and to 20.6(±3.4) at 24th week from 16.8 (±3.2) at baseline. GDS score reduced to 3.7 (±1.4) at 12th week and to 3.2 (±1.3) at 24th week from 4.3 (±1.5) at baseline. Only eight occasions of adverse event was reported (8.2%); no serious adverse event (SAE) were reported. Lost to follow up in the study was 14 (12.5%). Analysis of baseline data shows no significant difference. Their withdrawal seems to be unrelated to the adverse events and treatment outcome. Among the lost to follow up only one 1 (7.1%) had some side effect.* ***Conclusion:*** *Our study supports the pharmacokinetic rationale for the rivastigmine patch, indicating that smooth and continuous delivery of rivastigmine translates into an improved tolerability profile versus conventional oral administration, while maintaining clinical effectiveness.*

Key words: *Dementia, Alzheimer's disease, rivastigmine patch, tolerability, safety, MMSES, GDS*

Background:

Alzheimer's disease (AD) is the most common form of dementia. There is no cure for the disease, which worsens as it progresses[1]. Most often, AD is diagnosed in people over 65 years of age,[2] although the less-prevalent early-onset Alzheimer's

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can occur much earlier. In 2006, there were 26.6 million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050[3]. As life expectancy increases, Alzheimer becomes an important health problem for societies and causes significant impacts on family and community.

As the disease advances, symptoms can include confusion, irritability and aggression, mood swings, trouble with language, and long-term memory loss[4]. Gradually, bodily functions are lost, ultimately leading to death. Since the disease is different for each individual, predicting how it will affect the person is difficult. AD develops for an unknown and variable amount of time before becoming fully apparent, and it can progress undiagnosed for years. On average, the life expectancy following diagnosis is approximately seven years[1]. Fewer than three percent of individuals live more than fourteen years after diagnosis[6].

The cause and progression of Alzheimer's disease are not well understood. Research indicates that the disease is associated with plaques and tangles in the brain[7]. Current treatments only help with the symptoms of the disease. There are no available treatments that stop or reverse the progression of the disease. Clinical trials have been or are being conducted to find ways to treat the disease, but it is unknown if any of the tested treatments will work. Mental stimulation, exercise, and a balanced diet have been suggested as possible ways to delay symptoms in healthy older individuals, but they have not been proven as effective. Because AD cannot be cured and is degenerative, the sufferer relies on others for assistance. The role of the main caregiver is often taken by the spouse or a close relative. Alzheimer's disease is known for placing a great burden on caregivers; the pressures can be wide-ranging, involving social, psychological, physical, and economic elements of the caregiver's life[8].

Cholinesterase (ChE) inhibitors have been major treatment of Alzheimer's disease. Rivastigmine a member of Cholinesterase (ChE) inhibitors family have been shown to be effective in improving cognitive and global functioning in AD patients[9,10,11]. Rivastigmine is a selective, reversible acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitor. It could also be classified as a pseudo-irreversible cholinesterase inhibitor, as the duration of cholinesterase inhibition is longer than its elimination half-life[12].

The European Federation of Neurological Societies guidelines recommend considering the use of cholinesterase inhibitors in patients with severe disease, based on evidence of treatment benefit in these patients[13]. Current treatment guidelines recommend that the choice of therapy for patients with Alzheimer's disease be based on the tolerability profile and ease of use[14]. One of the primary objectives for AD treatment with cholinesterase inhibitors is to improve tolerability. Cholinesterase inhibitors enhance central cholinergic function, thereby increasing the availability of Achytylecholine (ACh) to stimulate nicotinic and muscarinic receptors within the brain[15].

Although cognitive symptoms of Alzheimer's disease can be managed with these pharmacological agents, treatment may be complicated by several factors, including the patient's age and concomitant conditions[16]. Cholinesterase inhibitors that are administered orally can sometimes lead to gastrointestinal AEs, particularly nausea and vomiting, which may prevent patients from achieving and maintaining optimal therapeutic doses in clinical practice. Patients with Alzheimer's disease are usually older individuals who are likely to receive concomitant medication for other conditions, which increases the risk of drug interactions and adverse events[17]. Treatment compliance in patients with Alzheimer's disease is particularly important as patients receiving regular treatment have a greater chance of slowing or delaying disease progression. As most patients with Alzheimer's disease require caregiver support for daily aspects of life, including managing and taking their medication, which results in caregiver stress and increased workload. Simplifying treatment regimens (once daily) and providing more patient and caregiver-friendly modes of administration would go a long way in improving adherence/ compliance[17].

One such mode of drug administration is transdermal delivery, which has the potential for providing continuous drug delivery and steady plasma levels, with minimal fluctuation between peak and trough plasma levels, thereby reducing adverse events and potentially minimizing voluntary noncompliance[18]. Moreover, by avoiding the gastrointestinal tract and the first-pass effect observed with oral administration, transdermal patches are likely to provide more predictable and reliable delivery of the drug[17]. In addition, patches may serve as visual reminders for patients or caregivers, offer visual reassurance that the medication is being taken and reduce the likelihood of accidental overdose[17]. The overall clinical benefit of transdermal patches is dependent on the balance between drug delivery, skin adhesion and skin tolerability[19,20].

Rivastigmine is well suited for transdermal delivery because of its low molecular weight and amphipathic properties, which allow it to pass easily through the skin to the bloodstream[21]. Although its precise mechanism of action is unclear, rivastigmine is believed to facilitate cholinergic neurotransmission by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis in functionally intact cholinergic neurons. Absorption of rivastigmine from the transdermal patch is slow, with rivastigmine being detected in the plasma after a lag time of 0.5–1 hour after the first dose[22]. Approximately 50% of the drug load is released from a patch during the 24-hour application period[23]. Peak plasma concentrations are reached in 10–16 hours after a single dose, with a slow decrease in concentration over the remainder of the 24-hour period[24].

Pharmacokinetic studies conducted with patch have shown that transdermal administration of rivastigmine prolongs tmax, lowers Cmax and reduces fluctuation in plasma concentration. The 10cm^2 rivastigmine patch provides equivalent exposure to the highest capsule dose, delivering optimal rivastigmine exposure to provide a therapeutic effect. The patch formulation has been evaluated by studies with rivastigmine patch, 10cm^2 and showed similar efficacy to the highest doses of rivastigmine capsules with three times fewer reports of nausea and vomiting. Caregivers also showed to prefer patch to the capsule. The patch was significantly preferred to the capsule with respect to ease of following the schedule and ease of use.

Current study aimed to evaluate efficacy, safety and tolerability data of rivastigmine patch, to assess patient compliance, to assess the change in cognitive and global outcome of treatment in patients with dementia (with probable Alzheimer's disease).

Methods:

Study subjects: A total of 112 dementia patients (with a diagnosis of probable Alzheimer's disease) from 12 centers were enrolled who were residing with someone in the communities throughout the study. Inclusion criteria for patients are a. Males and females not of child-bearing potential, b. Mini-Mental State Examination (MMSE) score of 10-26, c. Residing with someone in the communities throughout the study or living alone, in contact with the responsible caregiver every day, primary caregiver was willing to accept responsibility for supervising the treatment and condition of the patient throughout the study and providing input of efficacy assessment in accordance with all protocol requirements. Patients were excluded from the study if a. diagnosis of an active skin lesion that would prevent accurate assessment of the adhesion and potential skin irritation of the patch, b. history of allergy to topical products containing any of the constitution of the patches, c. evidence of severe or unstable physical illness (i.e., acute and severe asthmatic conditions, history of seizure, severe or unstable cardiovascular disorders, active peptic ulcer disease, clinically significant laboratory abnormalities or any patient with a medical condition which would prohibit them from completing the clinical trial), d. patient have bradycardia or sick sinus syndrome or conduction defects (sino-atrial block, second degree A-V blocks), e. body weight less than 40 kg and f. hypersensitivity to cholinesterase inhibitors.

Treatment exposure: After eligibility and baseline assessments, patients were entered a 24-week open label treatment phase. Baseline assessments include

vital signs, physical examination, inclusion/exclusion criteria, and concomitant medications history and drug indication. All patients were started with application of one 5 cm² patch, followed by an up-titration to the target dose of 10 cm² patch size. Starting on the day following the baseline visit, all eligible patients were given with one 5 cm^2 patch in the morning, for 24 hours. Patches were applied by the caregiver to the upper arm or the back area, on clean and dry skin with no cuts, rashes, or other skin problems. Placements were alternated from the right to the left side daily. After week 4 assessment, dosages were increased to the target patch size of 10 cm² with adjustments as necessary for safety and tolerability. The subjects were then maintained at their highest well-tolerated patch size for an additional 20 weeks. Compliance was assessed at each visit using information provided by the caregiver. Data regarding psychotropic medications was captured; any other concomitant medications and/or significant non-drug therapies applied to the patient throughout the trial were recorded.

Outcome assessment: Efficacy assessments were performed at weeks 12 and 24, and safety was monitored at all assessment points. There were provisions of the unscheduled visit if necessary. The primary endpoint is the proportion of patients treated by 10 cm² patch sizes for at least 8 weeks at week 24. Safety evaluations include vital signs, adverse events, concomitant medications and physical examination. Efficacy evaluations include the MMSE score, and the Global Deterioration Scale (GDS) score. The MMSE test consists of five sections and results in a total possible score of 30, with higher scores indicating better function. GDS is broken down into 7 different stages. Within the GDS, each stage is numbered (1-7), given a short title (No cognitive decline, very mild cognitive decline, Mild cognitive decline, Moderate cognitive decline, moderately severe cognitive decline, severe cognitive decline and Very severe cognitive decline).

Safety assessments were done based mainly on the frequency of adverse events. The adverse events were decided to be summarized by the number and percentage of patients in each primary system organ class and preferred term. Appearance or worsening of any undesirable sign, symptom, or medical condition occurring was considered as an adverse effect even if the event is not considered to be related to study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, with potential for study drug discontinuation or require therapy. An SAE was defined as an event which was fatal or life-threatening, might result in persistent or significant disability/incapacity constitutes a congenital anomaly/birth defect requires inpatient hospitalization or prolongation of existing hospitalization. Multiple occurrences of the same AE or SAE in the same patient were counted only once, using the worst severity and drug relationship.

The safety and efficacy variables were descriptively analyzed using summary statistics. The study was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki. Eligible patients were included in the study after providing written informed consent.

Results:

Baseline characteristics

A total of 112 patients were enrolled from twelve centers. Of them 98 (87.5%) completed study. Final analysis included 98 subjects. Analysis of baseline and available data until the drop out revealed no significant differentials. At enrollment average age of the patients was 68.9 (±8.7) years and 66.3% were male. 23.5% were of an age between 50 – 64 years, around 75% were of age between 65 - 85 years and 2% were aged over 85 years. Average weight of the patients was 61.8 (±7.7) kg. (Table 1)

Table-I

Patient characteristics

Age group	Frequency (%)
50 - 64 years	23 (23.5)
65 - 85 years	73 (74.5)
> 85 years	2 (2.0)
Sex Frequency (%)	
Male	65 (66.3)
Female	33 (33.7)
Age (n=98)	
Mean (SD)	68.9 (8.7)
Median (IQR)	68 (65 -75)
Weight	(n=98)
Mean (SD)	61.8 (7.7)
Median (IQR)	61 (56.2 - 61)

Treatment profile

All patients started treatment with the application of one 5 cm² patch, followed by an up-titration to the target dose of 10 cm² patch size. Rivastigmine 5 cm^2 patch size were loaded with 9 mg and providing 4.6 mg per 24 hour and 10 cm^2 patch size were loaded with 18 mg and providing 9.5 mg per 24 hour. At first visit 43.9% received 10 cm^2 patch, with upward titration 79.6% at 2ndvisit, 91.8% at third visit and 94.9% could receive 10 cm^2 patches. Concurrent medication was received by 25.5% patient at baseline, by 20.4% patient at 2ndvisit, by 17.3% patient at 3rdvisit and 16.3% patient at 4thvisit. Concurrent medication had to be changed in 17.3% patients at 2ndvisit, in 16.3% in 3rdvisit and 13.3% at 4thvisit (Table 2).

Efficacy assessment

Efficacy assessment was done in term of MMSE and GDS at 12thand 24thweek. Average MMES at base line was 16.8 (±3.2) units. At 12th week the average score increased to 19.3 (±3.1) unit and at 24th week it rose to 20.6(±3.4) (Table 3). Over the two assessments the average scores showed steady improvement from baseline (figure 1). Average GDS score at baseline was 4.3 (±1.5), the score reduced to 3.7 (±1.4) at 12thweek and to 3.2 (±1.3) at 24thweek. Average GDS score showed a decreasing trend from baseline towards the end of the study. GDS score is broken down into 7 different stages from 'no cognitive decline' to 'very severe cognitive decline'. Towards the end of the study the proportion of subjects with 'severe cognitive decline' or 'very severe cognitive decline' reduced to zero (Table 3).

Safety assessment

Appearance or worsening of any undesirable sign, symptom, or medical condition occurring was considered as an adverse event even if the event

Table-II

Treatment Profile

	Visit 1	Visit 2	Visit 3	Visit 4
Patch size				
5 cm	55 (56.1)	20 (20.4)	8 (8.2)	5 (5.1)
10 cm	43 (43.9)	78 (79.6)	90 (91.8)	93 (94.9)
Concurrent Medication				
Yes	25 (25.5)	20 (20.4)	17 (17.3)	16 (16.3)
No	73 (74.5)	78 (79.6)	81 (82.7)	82 (83.7)
Change in medication				
Yes		17 (17.3)	16 (16.3)	13 (13.3)
No		81 (82.7)	82 (83.7)	85 (86.7)

Results are presented in n (%)

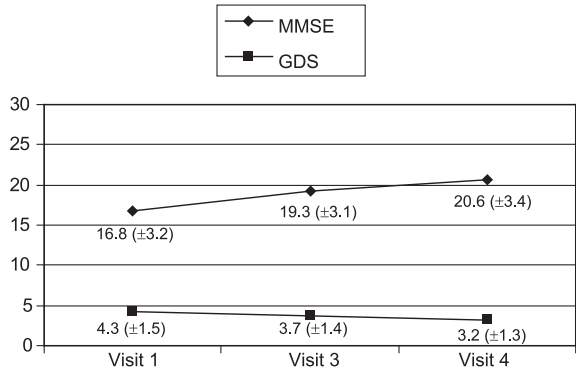

Fig.-1: *Efficacy assessment in terms of MMSE and GDS at 12thand 24thweek*

Table-III

Efficacy assessment in terms of GDS category

GDS	Baseline	week 12	week 24
No cognitive decline	12(12.2)	17 (17.3)	19 (19.4)
Very mild cognitive decline	1 (1.0)	0 (0)	6 (6.1)
Mild cognitive decline	3 (3.1)	7 (7.1)	15 (15.3)
Moderate cognitive decline	28 (28.6)	49 (50)	48 (49)
Moderately severe cognitive decline	37 (37.8)	22 (22.4)	10 (10.2)
Severe cognitive decline	14 (14.3)	3 (3.1)	0 (0)
Very severe cognitive decline	3 (3.1)	0 (0)	0 (0)

Results are presented in n (%)

is not considered to be related to study drug. Over all 8 (8.2% 95% CI 3.8, 19.9) person developed adverse event during the study period (AE) and none developed serious adverse event (SAE). At 2nd assessment (8thweek) none reported any adverse event. At 12th week follow up 6 (6.1% 95% CI 2.5-12.3) and at 24thweek follow up 2 (2.0% 95% CI 0.3 – 6.6) reported adverse events (Table 4). Systolic BP, diastolic BP and heart rate were assessed at all the four assessment points. No significant fluctuation in BP and heart rate was seen across the assessment points over the study period (table 5).

Table-IV

Adverse event

Adverse event	Visit 2	Visit 3	Visit 4	All visits
Yes	0 (0)	6 (6.1)	2 (2.0)	8 (8.2)
No	98 (100)	92 (93.9)	96 (98.0)	90 (91.8)

Results are presented in n (%)

Table-V

Systolic and diastolic BP and heart rate

	Visit 1	Visit 2	Visit 3	Visit 4
SBP	130.9 (13.2)	129.6 (11.6)	128.4 (10.2)	128.7 (9.6)
DBP	82.6 (6.4)	82.4 (4.9)	81.5 (4.9)	81.7 (3.9)
HR	75.4 (5.9)	74.8 (5.7)	74.5 (5.7)	74.7 (6.3)

Results are presented in mean (sd)

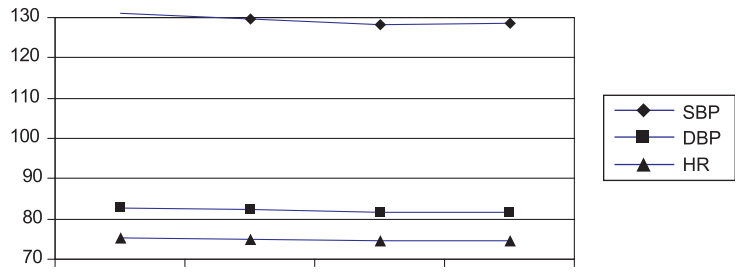

Fig.-2: *Trend in systolic and diastolic BP and heart rate*

Discussion:

One of the primary objectives of the study was to evaluate in a clinical practice setting the proportion of patients who can reach the target patch size of 10 cm^2 and our result shows that around 95% could receive 10 cm^2 patch size, showing a very high tolerability of the patch. In our study concurrent medication use also showed significant reduction to 16.3% patient in the end from 25% at baseline.

Rivastigmine is the first agent of its class to be developed as a transdermal patch and is indicated for the treatment of mild to moderate Alzheimer's disease in several countries worldwide. It is a low-molecular weight amphipathic molecule well suited for transdermal delivery. Prior experience with oral rivasigmine suggested that transdermal delivery of the agent had the potential for better tolerability, as strategies for reducing Cmax, delaying the time to Cmax and reducing the fluctuation index of oral rivastigmine were associated with reduced frequency and severity of gastrointestinal adverse events[12].

MMSE is a practical screening test for cognitive dysfunction[25]. The test consists of five sections namely orientation, registration, attention-calculation, recall, and language and results in a total possible score of 30, with higher scores indicating better function. In our present study efficacy of treatment in term of Mini-Mental State Examination (MMSE) at 12^{th} and 24^{th}week showed significant improvement. The Global Deterioration Scale (GDS) provides caregivers an overview of the stages of cognitive function for those suffering from a primary degenerative dementia such as Alzheimer's disease[26]. It is broken down into 7 different stages. Stages 1-3 are the pre-dementia stages. Stages 4-7 are the dementia stages. Beginning in stage 5, an individual can no longer survive without assistance. With the GDS, caregivers can get a rough idea of where an individual is at in the disease process by observing that individual's behavioral characteristics and comparing them to the GDS. Average GDS score showed a significant decreasing trend from baseline towards the end of the study. Studies have shown that the transdermal rivastigmine patch provides continuous drug delivery over 24 hours, with less fluctuation in plasma rivastigmine concentrations than oral rivastigmine administration and was associated with a generally better tolerability profile than that of oral rivastigmine. The efficacy of rivastigmine transdermal patch in patients with mild to moderate dementia of the Alzheimer's type was demonstrated in the large, 24-week IDEAL trial[27]. Patients receiving 24 weeks of treatment with rivastigmine transdermal patch in this study, experienced significant improvement in global and cognitive function, with the improvement in cognitive function being non-inferior to that observed with rivastigmine capsules. Moreover, most caregivers preferred the patch over the capsules, mainly because of the ease of following the schedule and the ease of use.

As the route of entry of the drug is skin, dermatological tolerability is a relevant issue to address. Rivastigmine patch had good skin adhesion, including in patients living in countries with hot and humid climates, and did not appear to interfere with normal daily activities[28]. The skin tolerability of rivastigmine patch was also favorable during the 24-week IDEAL trial and its 28-week open label extension, with <9% of patients/ evaluations experiencing severe application-site reactions during this period. Moreover, patients receiving rivastigmine patch appeared to be more likely to reach target dosages relative to patients receiving rivastigmine capsules, suggesting an advantage of the transdermal route of administration[29].

According the study finding only eight occasions of adverse event was reported (8.2%) no serious adverse event (SAE) were reported. Appearance or worsening of any undesirable sign, symptom, or medical condition occurring was considered as an adverse effect even if the event is not considered to be related to study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, with potential for study drug discontinuation or require therapy. Most adverse events were gastrointestinal and of mild to moderate intensity. Mostly nausea and few vomiting episodes were reported. None of the study discontinuation was reported due to adverse effect. No fluctuation in BP and heart rate

was seen either across the assessment points over the study period.

Adverse events associated with orally administered cholinesterase inhibitors are likely during the titration phase, which are believed to be caused by the rapid increase in ACh levels in the CNS[18]. Transdermal rivastigmine patch provide continuous delivery of the drug, thereby reduce fluctuations in plasma levels and potentially reduce the incidence of adverse events[12]. There have been reports of deterioration of fine motor behavior in patients with Alzheimer's disease during treatment with cholinesterase inhibitors[30]. However, rivastigmine transdermal patch applied once daily was not associated with impairment of complex movement performance in patients with Alzheimer's disease in a 42-day study[31]. Comparison of the pharmacokinetics of rivastigmine transdermal patch with those of oral rivastigmine revealed the patch being favorable for human condition[32]. Absorption of rivastigmine from the transdermal patch is slow, with rivastigmine being detected in the plasma after a lag time of 0.5–1 hour after the first dose[26].

One important limitation of the series is that the lost to follow up was 14 (12.5%). We analyzed the baseline data of those of the lost to follow up cases and also their available data before they left. Their withdrawal seems to be unrelated to the adverse events and treatment outcome. Among the lost to follow up only one 1 (7.1%) had some side effect.

In summary, the patch was generally well tolerated in trial setting regardless of concomitant treatment, with most treatment-emergent adverse events being mild to moderate in severity. Moreover, according to this analysis, patients receiving rivastigmine patch appeared to be more likely to reach target dosages. Our study supports the pharmacokinetic rationale for the rivastigmine patch, indicating that smooth and continuous delivery of rivastigmine translates into an improved tolerability profile versus conventional oral administration, while maintaining clinical effectiveness. This may allow patients easier access to optimal therapeutic doses, potentially improving the effectiveness of treatment. A transdermal patch may be the optimal way of delivering rivastigmine in the pharmacological treatment of AD. Well designed additional studies, including direct head-to-head comparisons, would help to confirm these results in line with the published clinical data.

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Therapeutic Modulation of Brain Temperature: Relevance of Hypothermia to Inflammatory Changes following Transient Cerebral Ischemia in Rats

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Abstract:

Background : *In stroke, the ischemic crisis activates a series of events, including the inflammatory reactions that are potentiated by reperfusion, eventually leading to neuronal damage. Mild hypothermia has been considered to have a protective effect during ischemic neuronal cell death. The chief aim in this study was to investigate whether changing temperature during and after ischemia could minimize this damage by reducing the inflammatory injury.* ***Material and Methods:*** *The effect of moderate whole body hypothermia (30^0 C) on transient focal cerebral ischemia induced inflammatory injury was investigated. Experimental stroke (transient focal cerebral ischemia) was induced by a 2-hour middle cerebral artery occlusion (MCAO) with the use of a suture inserting into the lumen of the internal carotid artery (ICA) in male Wistar rats. Histopathological evaluation was performed 96 h after reperfusion.* ***Results:*** *MCAO induced inflammatory injury, involving the ipsilateral cortex and basal ganglia with massive infiltration of neutrophils, macrophages and microvascular proliferation, was exhibited in all normothermic rats. However, hypothermic MCAO rats showed minimal inflammatory response.* ***Conclusion:*** *The present study provides experimental evidence for the beneficial role of mild hypothermia using reversible MCAO in rats. Our results indicate that moderate hypothermia has a significant protective effect on the inflammatory injury induced by transient focal cerebral ischemia. Perhaps, the therapeutic effect was related to a reduction in releasing of cytotoxic products and improvement of the cerebral microcirculation.*

Key words: *Focal cerebral ischemia; Transient middle cerebral artery occlusion; Hypothermia; Inflammatory reactions; Rats*

Abbreviation*: MCAO (middle cerebral artery occlusion), MCA(middle cerebral artery), ICA(internal carotid artery), CCA(common carotid artery), ECA(external carotid artery),*

Introduction:

Cerebral ischemia and reperfusion occur frequently either after brain surgery and open heart surgery or after spontaneous thrombolysis and breakup of cerebral emboli in common clinical events. Recirculation affects cerebral ischemia and modifies postischemic events in various ways. There is abundant evidence that an acute inflammatory reaction associated with ischemia and reperfusion contributes to the development of neuronal damage in stroke[1-8]. It has been believed that cytokine production and molecular adhesive events that occur early in ischemia and the subsequent extensive recruitment of leukocytes to the ischemic zone during reperfusion lead to inflammatory injury[9-11]. Initially, ischemia triggers the expression of a number of cytokines, which attract leukocytes into ischemic sites and stimulate the synthesis of adhesion molecules, such as ICAM-1 on migrated leukocytes, endothelial cells, and other types of cells. The upregulation of these inflammatory mediators occurring during ischemia promotes blood-borne inflammatory cell adherence and infiltration during reperfusion. Consequently,

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postischemic leukocytes exacerbate brain injury by physically obstructing capillaries to reduce blood flow during reperfusion and/or releasing cytotoxic products once migrated into the brain parenchyma[12-13].

Ischemic brain temperature is an important determinant of the structural and functional outcome of neuronal and cerebrovascular injury in animal models of experimental stroke[14, 15]. However, the effects of temperature on cerebral ischemia are uncertain. While moderate reductions in ischemic brain temperature provide histopathological protection[16, 17], elevation in ischemic brain temperature has shown to aggravate outcome[18, 19]. Again, it has been suggested a detrimental effect of severe hypothermia (25.9^{0}C) or prolonged hypothermia (48 h) on focal brain ischemia. Brain tissue undergoes cell death, including neurons and glial cells, in conjunction with infiltration of neutrophils, macrophages and microvascular proliferation[1-8].

To our knowledge, there are a few studies that examine the protective effects of moderate hypothermia induced during and immediately after transient focal cerebral ischemia, though, those are not conclusive. In the present study, we used the intraluminal model of transient middle cerebral artery occlusion (MCAO) in the rat to investigate the effect of moderate hypothermia on the inflammatory injury in the ischemic area. Our result shows that moderate hypothermia significantly reduces the inflammatory changes induced by transient focal ischemia.

Materials and Methods

Animals

Male Wistar rats (weighing 270 – 300 g; n=24) were housed in the same animal care facility with food and water available during a 12-hour light/ dark cycle throughout the protocol. MCAO was done by advancing a 4-0 surgical nylon suture into the internal carotid artery (ICA) to block the origin of the MCA[20-22]. Rats were fasted overnight before surgery but allowed to free access to water. Animals were anesthetized and maintained with 1.0 – 2.0% halothane in 70% N_2O and 30% O_2 using a face mask. The right femoral artery was cannulated to measure blood gas and blood glucose level before ischemia. Arterial pressure was monitored prior to MCAO and throughout the period of ischemia, and continuously for 20 min after the onset of reperfusion in all animals. Rectal temperature was controlled with a electrical heating pad to maintain the body temperature. All rats were randomly divided into two groups: Group I (Normothermic): MCAO was done at 37^{0}C body temperature (n-10); Group II (Hypothermic): MCAO was induced at 30^{0C} body temperature and hypothermia was maintained throughout the 2 h of ischemia and for an additional 1 h of reperfusion (n=14). The 30^{0}C whole body temperature was instituted 30 min prior to the surgery by spraying alcohol on the skin and fanning room air (20-20^{0}C) toward the animal's body. Then, animals were rewarmed to 37^{0}C using the heating pad

Ischemia (Surgical Procedures)

A 2 cm incision was made at the center of the neck, and the right common carotid artery (CCA), the external carotid artery (ECA), and ICA were exposed through a careful dissection under an operating microscope (Carl Zeiss, Inc., Thornwood, NY, USA). Further dissection was done to identify the pterygopalatine branch. The CCA and ICA were temporarily clamped using microsurgical clips (Codman & Shurtleff, Inc., Randolf, MA, USA). A 5-0 silk suture was tied loosely at the origin of the ECA and ligated at the distal end of the ECA. Then, a 4-0 surgical nylon suture, with its tip rounded by heating near a flame, was introduced into the ECA lumen through a small puncture. The silk suture around the ECA origin was tightened around the intraluminal nylon suture to prevent bleeding, and the microsurgical clips were removed. A length of 18.5 – 19.5 mm of nylon suture, determined according to the animal's weight, was gently advanced from the ECA into the lumen of the ICA until the suture blocked the origin of the MCA. The incision was temporarily closed using skin clips. In both normothermic (Group I) and hypothermic (Group II) animals, halothane anesthesia was maintained throughout the 2 hr of ischemic period and 1 h recirculation to allow accurate temperature control. After 2 h of ischemia, reperfusion was done by withdrawal of the suture until the tip cleared the ICA lumen and reached the origin of ECA.

Additional rats were used to measure body and regional brain temperature during ischemia a recirculation in normothermic (n=3) and hypothermic rats (n=3), without histopathology endpoint. Thirty minutes prior to MCAO, microthermocouples (100 mm) placed into a 27 gauge needle were inserted into the right (lesion side) and left (control side) cortex, caudate putamen, and preoptic areas through 1 mm burr holes in the skull. Brain and rectal temperature were recorded every 5 minutes throughout the experiment using a digital thermometer (Physitemp, Clifton, NJ, USA).

Tissue Preparation

Three days after MCAO, rats were anesthetized with intramuscular ketamine (44 mg/kg) and xylazine (13 mg/kg), and transcardially perfused with heparinized saline and 10% neutral buffered formalin. The head was further fixed in formalin solution for 1 h and then the brain was removed. The brain was cut into 2 mm thick coronal blocks. The brain tissue was processed, embedded, and 6 mm thick paraffin sections from each block were cut and stained with hematoxylin-eosin. Inflammatory injury was evaluated using light microscopy. The right hemisphere was divided into four anatomically distinct regions for detailed histological analysis . Inflammatory response, summation of infiltration by neutrophils, macrophages, and increased numbers of microvessels were evaluated in each distinct region by means of grading scaled presented in Table I. The severity of inflammation was factored into numerical grading. Multiple histological changes within a region were averaged.

Table-I

Brain ischemic damage grading scales

	Grade
Neutrophils	0: not detectable
	1: polymorphonucleus detected
Macrophages	0: not detected
	1: peripheral nucleus with cytoplasmic granules detected
Vasculature	0: normal
	1: increased number of microvessels

Statistics

Wilcoxon two-sample tests were performed to compare the response of inflammation between the normothermic and hypothermic MCAO rats. All data are presented as mean ±SD.

Results:

Blood gas values and serum arterial glucose levels before MCAO were within normal ranges (Table II). The blood pressure fluctuated within 5-10 mmHg during surgery. There were no detectable differences in arterial blood pressure values prior to vessel occlusion and 1 h after the surgery in both normothermic and hypothermic rats. Two animals died 24 h after surgery. The rectal temperatures were maintained almost constant at 37^0C in normothermic and 30^0C in hypothermic rats (Fig. 1). Prior to ischemia, brain temperature was elevated above the rectal temperature by 0.5^0C in normothermic animals and 1.5^0C in hypothermic rats. After the onset of MCAO, brain temperature declined approximately 0.5^0C and fluctuated at 37.2 ±0.7 and 31.2 ±0.6^0C in normothermic and hypothermic animals, respectively.

Table-II

Serum arterial blood gas, glucose, and blood pressure (BP) values

	pH	PCO_2	PO_2	Glucose (mg/dl)	BP (mmHg)	
					Before	1 h After
Gr I	7.41 ±0.07	35.8 ±1.9	139 ±19.9	131 ±29.2	97 ±6.5	95 ±3.2
Gr II	7.33 ±0.04	41.0 ±4.9	191 ±21.7	117 ±14.1	110 ±7.8	101 ±1.9

There were massive infiltration by neutrophils and macrophages as well as increased numbers of microvessels, compared to the contralateral side, were detected in the lesioned region. Figure 1 summarize the inflammatory responses in each of the four regions in both the normothermic and hypothermic ischemic rats. Significant differences were detected between the normothermic and hypothermic animals for inflammatory changes in all the regions ($p<0.01$).

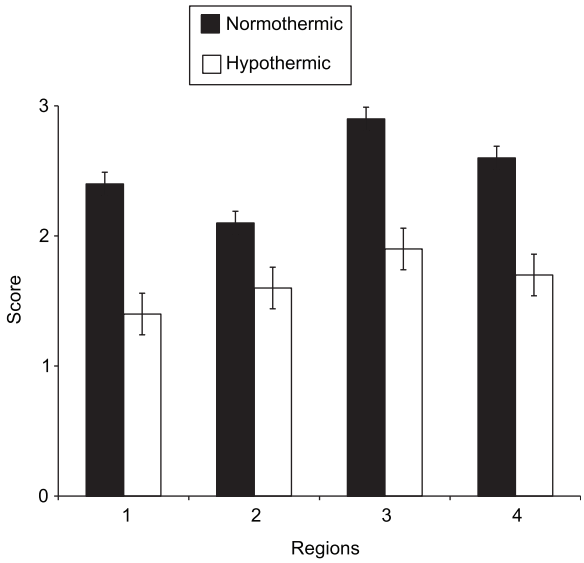

Fig. -1: *Bar chart presents the mean ±SE of inflammatory responses in normothermic MCAO and hypothermic MCAO in the four different brain regions. Region 1: Parietal cortex, 2: Piriform cortex, 3: Caudate putamen and 4: Preoptic area*

Discussion:

In the present study, the therapeutic value of temperature on the transient focal ischemia induced inflammatory injury in the ischemic territory was tested. Our data demonstrated that moderate whole-body hypothermia significantly reduces the degree of inflammatory changes after transient focal cerebral ischemia in the rat.

An extracranial approach to occlude the MCA, by introducing a suture into the ICA, has been recently developed [20-22]. One of the major advantages of this model is focal cerebral ischemia can successfully be induced without opening the cranium. Again, reperfusion can be easily induced by simply withdrawing the suture. The degree of tissue damage and mortality rate is a function of duration ischemia and reperfusion time. We used 2-h duration of ischemia to avoid mortality and 72 h reperfusion time to allow for maturation and clear demarcation of the injury. Our normothermic animals showed a sharply demarcated, reproducible ischemic lesion localized in the frontopareital cortex and basal ganglia (data not presented in this paper). This model of ischemia in our hands is reproducible and allows for detailed histopathological evaluation of ischemic cell damage and therapeutic intervention. Moreover, this model mimics closely the clinical situation because the MCA is the most frequently embolized artery, and recirculation occurs as recanalization is induced surgically or pharmacologically or as a result of spontaneous recanalization.

Because of the minimal lesion, and consequently the absence of a clearly defined infarct in the hypothermic animals, we adapted a scoring system for differential cellular evaluation in four anatomically distinct brain sub regions. Measuring only the area or volume of the lesion fails to demonstrate the anatomical sensitivity and distribution of an ischemic lesion. The present scoring system provides a detailed evaluation of the anatomical distribution of the cellular response and confirms the presence of a reproducible lesion localized at the neocortex and basal ganglia after MCAO.

Hypothermia reduces the cerebral ischemia induced inflammatory responses in the ischemic territories in the present study; though the exact mechanism of hypothermic protection in cerebral ischemia remains unknown. Ischemia induced neurotransmitter release, cerebrovascular permeability, as well as hemodynamic and metabolic abnormalities have been shown to be both temperature-sensitive and associated with ischemic cell death. It has been believed that normothermic MCAO induces a regional reduction in cerebral blood flow and development of a localized cerebral infarction[23]. Brain tissue undergoes cell death, including neurons and glial cells, in addition to infiltration of neutrophils and macrophages and

microvascular proliferation[24]. The impact of pro-apoptotic transmembrane protein that can transduce cell death signal is not overruled during cerebral ischemia[25]. Phanithi et al[26] has suggested that mild hypothermia provides protection by reducing the expression of such fatal protein, thereby mitigating the apoptotic neural death. Additionally, it has been suggested that mild hypothermia can significantly reduce neuronal damage by promoting survival, after reversible MCA occlusion.

Furthermore, the protective effect of moderate hypothermia has been attributed, to a greater extent, to a decreased metabolic rate[27], decrease in adenosine triphosphate (ATP) depletion[28], protein synthesis inhibition[29], reduced post-ischemic free radical production[30], increase cerebral blood flow, and reduced neurotransmitter release[31,32]. Whatever the mechanism in the protective action of moderate hypothermia, the present study was limited to inflammatory responses and it stresses the need for further investigation to explore the mechanism.

In conclusion, our data demonstrate that transient ischemia induced by using the intra-arterial suture method to occlude the MCA results in a reproducible brain injury and that moderate hypothermia has a profound protective effect on the inflammatory brain injury after transient MCAO.

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Juvenile Myasthenia Gravis: A Case Report and Review of Literatures

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Abstract:

Juvenile myasthenia gravis (JMG) is a rare autoimmune disorder of childhood. Pediatric presentation of MG is more common in Oriental than in Caucasian populations. JMG need to be differentiated from congenital myasthenia gravis which do not have haan autoimmune basis. An 11 years old girl presented with drooping of eye lids which was more marked at the later part of day and was gradually progressive . She had complained of double vision. She had no family history of myasthenia gravis. Ice pack test, repetitive nerve stimulation test, and anti acetylcholine receptor antibody test support the diagnosis. She was treated with pyridostigmine and was started as 30mg four times daily and increased to 60 mg/qds. Subsequently her symptoms improved gradually and she became stable.

Key word: *Juvenile myasthenia gravis (JMG). myasthenia gravis (MG)*

Abbreviation: *JMG(Juvenile myasthenia gravis). MG (myasthenia gravis), NMJ (neuromuscular junction), CMG (congenital MG), AchRA (Acetylcholine receptor antibody), MuSK (muscle specific kinase)*

Introduction:

Myasthenia Gravis (MG) is an autoimmune disease in which antibodies are directed at the postsynaptic membrane of the neuromuscular junction (NMJ), leading to varying degrees of muscle weakness and fatigability. Where MG presents before 19 years of age, it is termed juvenile myasthenia gravis (JMG) [1]. JMG is a rare disorder of childhood and has many clinical features that are distinct from adult MG. Pediatric presentation of MG is more common in Oriental than in Caucasian populations [2]. Up to 50% of all cases of MG in Chinese populations present in childhood, mostly with ocular features, with a peak age at presentation of 5-10 years [3]. MG occurs as one of three subtypes; transient neonatal, congenital, or juvenile MG. One half to 2/3 of these children are not diagnosed within the first year of disease onset [4]. Autoimmune antibodies are directed against the postsynaptic membrane of the neuromuscular junction, resulting in muscle weakness and fatigability. Prepubertal children in particular have a higher prevalence of isolated ocular symptoms, lower frequency of acetylcholine receptor antibodies, and a higher probability of achieving remission. Diagnosis in young children can be complicated by the need to differentiate from congenital myasthenic syndromes, which do not have an autoimmune basis. Treatment commonly includes anticholinesterases, corticosteroids with or without steroid-sparing agents, and newer immune modulating agents. Plasma exchange and intravenous immunoglobulin (IVIG) are effective in preparation for surgery and in treatment of myasthenic crisis. Thymectomy increases remission rates. Diagnosis and management of children with JMG should take account of their developmental needs, natural history of the condition, and side-effect profiles of treatment options.

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Case report:

Miss Ishrat Jahan, 11 years old girl with non-consanguineous parents, presented with the complaints of asymmetric dropping of upper eyelid for two months. Drooping was less apparent in the morning and worsened at the later part of day. She had also complaint of double vision on looking to lateral side. On enquiry she mentioned of difficulties in chewing food at the later part of intake. She had no nasal regurgitation and did not complain of any significant weakness while using limbs above the shoulder, getting up from the squatting position or climbing stairs. She had not complained of muscle pain or tenderness, skin rash or joint pain. On general examination no deviation from normal is noted. On neurological examination incomplete ptosis was noted, more on the right. Range of eye movement was normal. Pupil size was normal and equal on both sides and reacting normally to light. Examination of fundus and lower cranial nerves was found to be normal. Motor, sensory and cerebellar examination also revealed no abnormality. Bedside ice pack test was done and the test was found to be significant (on the right palpabral fissure width was increased about 6 mm and on the left it was about 5 mm).

Complete blood count with ESR, CxR (PA view), chest CT, thyroid profile and ANF were normal. Repetitive nerve stimulation showed 25% decrement of response at deltoid, 16% in ADM, 42% in orbicularis occuli (Fig-I, 2). The test is positive for post-synaptic neuromuscular junction disease. Anti-acetylcholine receptor antibody test report was highly positive (26.30, positive >0.4). She was diagnosed as a case of juvenile myasthenia gravis. Pyridostigmine was started as 30mg four times daily and increased to 60 mg/ qds. Subsequently her symptoms improved gradually and she became stable.

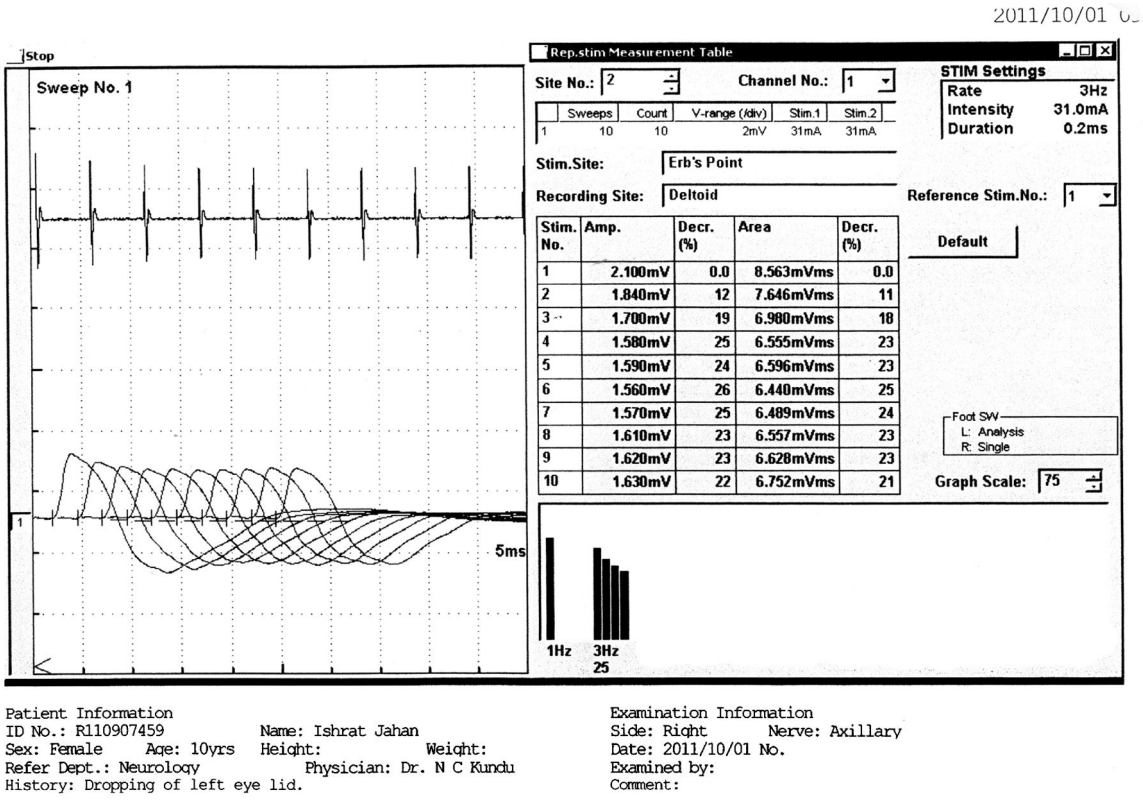

Fig-1: *Repetitive nerve stimulation at Erb's point (recording site deltoid)*

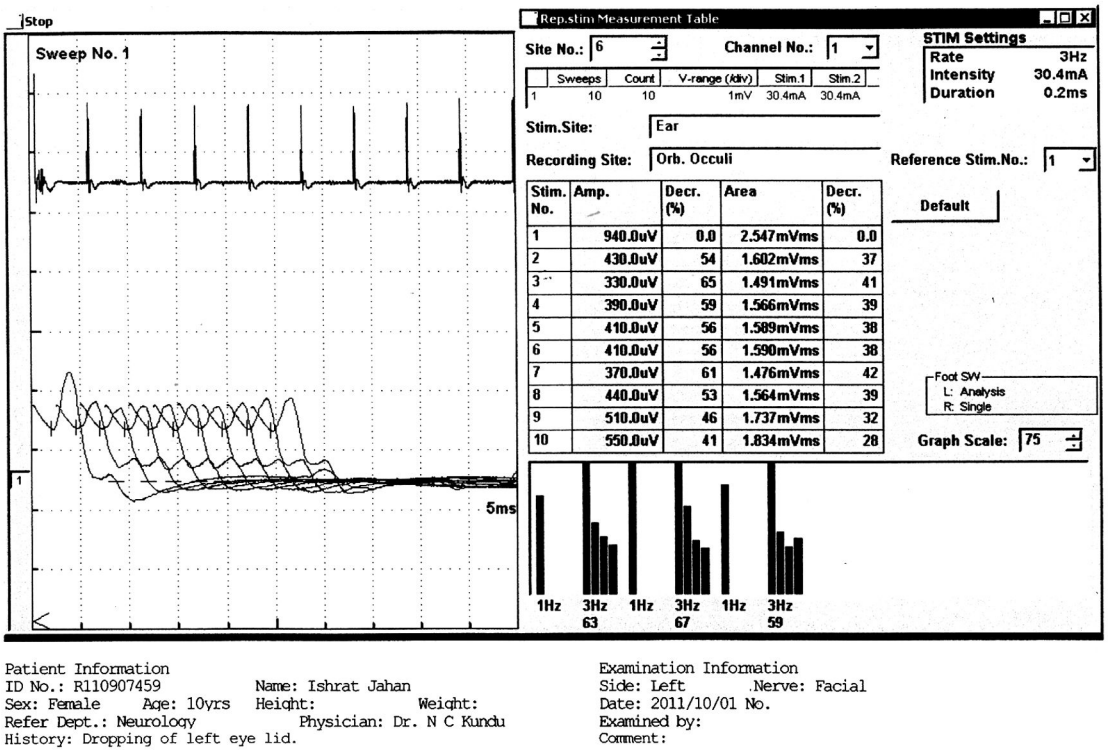

Fig-2: *Repetitive nerve stimulation at Ear (recording site orbicularis Occuli)*

Discussion:

Transient neonatal MG usually occurs in newborns, born to mothers with MG due to passive transmission of abnormal antibodies through the placenta [5]. This disorder differs from the rare cases of congenital MG (CMG), in which children have episodic apena and weakness of extra ocular, pharyngeal and respiratory muscles [6]. They inherit defects to the neuromuscular synapse, so they rarely have elevated levels of AchRA [5].

JMG is the most common type of pediatric MG and the present case has exhibited this subtype. It is similar to the adult autoimmune disorder, but children often exhibit more severe symptoms. Prepubertal children presenting with JMG have some interesting and distinct clinical features compared with those developed JMG around or after puberty [7-8]. Prepubertal JMG is more likely to manifest as ocular myasthenia [9]. There is an equal male to female ratio, in contrast to the female predominance seen in peri or postpubertal children. It also shows better prognosis, with a higher rate of spontaneous remission [7-10]. Peri or postpubertal patients presenting with JMG share more similarities with adult onset MG.

JMG is primarily diagnoses by clinical features. A number of diagnostic tools are available to aid diagnosis. An antibody to AchR supports the diagnosis of JMG. In this patient AchR antibody was done and showed high titer. Children who are negative for AchR antibodies can lead to difficulty in differentiating from CMG. Variable percentages (0-49%) of MG patients without AchR antibodies are found to have antibodies against another neuromuscular junction protein, the muscle specific kinase (MuSK) [11]. MuSK positive MG is rare in children and represents a distinct subgroup of JMG, more severe disease with prominent facial and bulbar weakness and frequent respiratory crises [12]. Electrophysiology testing is invaluable in investigations of suspected JMG. Repetitive nerve stimulation will show a decrement in compound

muscle action potential of > 10% by the 4th or 5th stimulation. Single fiber EMG (SFEMG) is especially useful in the diagnosis of seronegative MG and congenital myasthenic syndromes. Sensitivity for neuromuscular disorders is 97% and thus a normal result makes a diagnosis of myasthenia very unlikely [13-14]. In this reported case RNS was done and revealed 25% decremented response at deltoid, 16% in ADM and 42% in orbicularis occuli muscle.

Although thymoma in children is rare, the thymus must be imaged once JMG has been diagnosed. Thymic hyperplasia is the commonest abnormality of the thymus in JMG [15].

But X-ray chest and CT scan of chest of this patient revealed no abnormality.

Management of children with JMG should be delivered by a multidisciplinary team. Treatment has largely been extrapolated from adult studies and experience with adult patients. Side effect profiles and considerations are not always directly comparable between adult and pediatric population.

Acetylcholinesterase inhibitors are the first line treatment in JMG and provide symptomatic relief. Pyridostigmine is commonly used and is tailored to effects. Cautious use in MuSK positive children is advised because of risk of acetylcholine hypersensitivity [16]. Immunosuppression and immunomodulation is required to improve symptoms of JMG in most patients. Corticosteroids are effective and are the mainstay of therapy, can worsen symptoms if started at high doses [17]. Because of numerous adverse effects associated with long term use of steroids, steroids are often used in combination with steroid sparing agents. Azathioprine has been found to be effective. It can be used singly or in combination with steroid. Beneficial effects may take months to be seen [18]. Patients unresponsive or intolerant to azathioprine should be considered for other immunosuppressive agents including cyclosporin or cyclophosphamide [19-20]. A Cochrane review suggests that cyclosporine either as monotherapy or with corticosteroids, or cyclophosphamides in conjunction with steroids improve symptoms of MG within 1 year [21]. A recent retrospective study which includes children as well concluded that Mycophenolate mofetil (MMF) when used as monotherapy or in conjunction with steroids is effective. Maximum effects may not be seen until after one year of treatment [22]. Tacrolimus has shown early and sustained improvement of symptoms in MG, allowing dose reduction of prednisolne and in many cases its complete withdrawal. These steroid sparing effects were seen within 6 months [23-24]. Rituximab has been used in refractory JMG [25].

Recent reviews of children including prepubertal patients, suggested increased remission rates after thymectomy. Caution needs to be taken in early childhood due to subsequent immunosuppression and the high rates of spontaneous remission in prepubertal presenters [26-27]. Current evidence suggests that thymectomy should not be recommended in MuSk positive disease as it is unclear whether it confers any benefit [28-29]. Thymectomy in pure OMG is controversial. Thymectomy is not proven to reduce risk of progression of OMG to generalized JMG and is not routinely indicated in pure OMG in children but has been performed in refractory cases [30].

Outcome:

Outcomes in JMG have improved significantly over last decades, with better recognition, diagnosis, and more effective therapies, and long term prognosis is good [31]. Children with JMG exhibit higher rates of remission than adults. This includes spontaneous remission and remission following a period of drug therapy. Prepubertal children have the highest rates of spontaneous remission.

Summary:

JMG is a rare, autoimmune disorder of childhood that share many characteristics with the adult form of the disease. However, as described, there are many important aspects that are specific to the pediatric population. So, diagnosis and management of children with JMG should take account of their developmental needs, natural history of the condition, and side-effect profiles of treatment options.

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Carotid atherosclerosis in diabetic patients with Ischemic Stroke: an experience at BIRDEM

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Abstract:

Background and objectives: *Carotid atherosclerosis constitutes an important cause of ischemic stroke. Type 2 diabetes mellitus is known to be an independent risk factor for stroke and its recurrence. This study was aimed to explore relationship between carotid atherosclerosis and ischaemic stroke in patients with diabetes and its association with other risk factors.* ***Materials and Methods:*** *A total number of 50 ischemic stroke patients, as confirmed by CT/MRI, patients with type 2 diabetes mellitus, of both sexes, age range 40-79 years, were recruited in the study from in-patient Neurology department, BIRDEM. Carotid duplex study was done. Ischemic Stroke patients were sub grouped into normal, mild (<2), moderate (2-4) and severe (>4) on the basis of ICA/CCA flow velocity ratio. Blood glucose and fasting lipid levels and blood pressure were recorded. Lipid abnormality ,LDL 130mg/dl, total cholesterol 200 mg/dl was defined following NCEP and AHA guidelines. Data were collected in a pre-formed printed case record form and analyzed using SPSS software.* ***Results:*** *Of the 50 cases only 9 (18%) had normal ICA/CCA flow velocity ratio. Their mean age was 48.0±4.4 years. Three (6%) cases had severe form of ICA/CCA flow velocity ratio 47.67±2.08. Subjects with stroke having mild to moderate compromised flow velocity ratio were significantly older (p<0.001). Mean (±SD) total cholesterol and LDL-cholesterol were significantly associated with ICA/CCA flow velocity ratio (p<0.001 for both) in the study subjects. Serum triglyceride did not show significant association with ICA/CCA flow velocity ratio. Uncontrolled diabetes mellitus (p=0.02) and blood pressure (p=0.001) shown to be significantly associated with atherosclerotic changes in the study subjects.* ***Conclusions:*** *The data conclude that diabetic patients with ischemic stroke have carotid atherosclerosis which is significantly related with lipid abnormality. High total cholesterol and LDL cholesterol are associated with degree of carotid atherosclerosis. Study subjects with severe atherosclerotic changes are relatively younger in age. Carotid duplex study should be planned in ischemic stroke patients with diabetes which will identify the individual at risk and suggest them necessary prevention program.*

Keywords: *Diabetes mellitus, ischemic stroke, carotid atherosclerosis, lipid abnormality.*

Introduction:

Stroke is the third leading cause of death and disability in western countries. The very basic vascular pathology remained to be atherosclerotic changes and resulting stenosis of the internal carotid artery[1,2]. Stenosis is suggested to alter the perfusion to the brain owing to reduction of diameter of the carotid artery or leaving potential site for thrombi originating from plaques at the site of stenosis[3].

Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes,

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who also have twice the risk of stroke or heart disease and a greater prevalence of atherosclerosis than patients than who are not diabetic[4]. Diabetes mellitus plays a crucial role as an independent risk factor for stroke in 37-42% of cases, especially among patients younger than 65[5] years. It has also been determined that the increased frequency of dyslipidaemia, hyperglycaemia, obesity, hypertension and associated nephropathy may contribute to accelerated atherogenesis in diabetic subjects[6]. Epidemiological data have demonstrated that the risk of coronary heart disease and other forms of atherosclerotic vascular diseases rise in those with high plasma cholesterol level and in particular the high ratio of total cholesterol to LDL-cholesterol. A much weaker correlation also found to exist with plasma triglyceride level. Extensive large-scale randomized trials have shown that LDL and total cholesterol level below the target values reduces the risk of cardiovascular events including death, myocardial infarction and stroke, and also reduces the need for revascularization[7].

Identification of carotid stenosis and addressing the risk factors with appropriate medical intervention claimed to reduce the risk of stroke in diabetic patients. Duplex ultrasonography of the carotids is a useful diagnostic tool for the detection of carotid stenosis and its diagnostic value increases in individuals with presence of other risk factors. Although diabetes is a recognized risk factor for ischemic stroke, data are lacking about the involvement of carotid artery stenosis in stoke patient with diabetes mellitus. Hence the present study was undertaken to evaluate internal carotid artery and common carotid artery flow velocity ratio and explore its relationship in diabetic patients with ischaemic stroke.

Materials and Methods:

This cross-sectional observational study was conducted in the Department of Neurology, BIRDEM. Fifty (50) ischemic stroke patients of both sexes, confirmed by imaging (CT/MRI), with type 2 diabetes mellitus, age range 40-79 yrs, not on lipid lowering agents, were consecutively recruited in the study during the period of June 2010 to December 2010. Patients with hemorrhagic stroke, other complications and absence of diabetes were excluded. Written consent was obtained from close relations of the patient(s). Duplex study of neck vessels was performed and subjects were classified as normal (no alteration of flow velocity), mild (<2), moderate (2-4) and severe (>4) carotid atherosclerosis on the basis of ICA/CCA flow velocity ratio[8]. Blood glucose, fasting lipid levels and blood pressure were recorded. Total cholesterol and LDL cut-off values were 200 mg/dl and 130 mg/dl respectively following National Cholesterol Education Program (NCEP) and American Heart Association (AHA) guidelines. Variables of interest for the study were recorded in a predesigned case record form. Statistical analyses were performed using Statistical Package for Social Science (SPSS) Version 15 for Windows. Data were expressed as mean±SD and number (percent) as appropriate. One way ANOVA were performed as applicable. P value <0.05 was taken as level of significance.

Results:

Of the 50 study subjects 28 (56.0%) were male and 22(44.0%) female. Distribution of male female subjects on the basis of ICA/CCA flow velocity was shown in table 1. The distribution did not show significant association (p=0.37).

Of the 50 subjects 18%, 52%, 24% and 6% had normal, mild, moderate and severe carotid atherosclerotic disease as judged by ICA/CCA flow velocity (Table 2). Mean (±SD) age (yrs) of subgroup of patients was 48.00±4.44, 56.31±4.36, 58.50±8.47 and 47.67±2.08 respectively. This mean age distribution showed significant association (p<0.001).

Mean (±SD) triglyceride levels of the study subjects was 194±52. In the four subgroups the values were 163±10, 196±59, 217±52 and 175±13 which did not show any statistical significant association (Table 3).

Mean (±SD) total cholesterol level of the study subjects was 236±38. In the different subgroups on the basis of ICA/CCA flow velocity mean total cholesterol level was significantly higher (Table 3). The value was 176±14, 233±13, 275±15 and 296±12 for normal, mild, moderate and severe groups respectively (p<0.001) (Table 3).

Mean (±SD) LDL cholesterol of the total subjects was 124±22. In the different subgroups on the basis of ICA/CCA flow velocity mean total cholesterol level was significantly higher. The value in the four sub-groups was 105±21, 109±14, 144±10 and 157±6 respectively (p<0.001) (Table 3)

Of the 50 in 17 subjects blood pressure was controlled and of them ICA/CCA flow velocity was normal in 8 (47%) and 6 (35.3%) and 3 (17.6%) mild and moderate atherosclerosis disease. Among those with uncontrolled blood pressure ICA/CCA flow velocity was normal in 2 (3%). And 20 (60.6%), 9 (27.3%) and 3 (9.1%) patients had mild moderate and severe atherosclerosis (Table 4). This distribution showed statistical significant association (p=0.001) (Table4).

Of the 50 subjects diabetes was in control among 18 (34.6%) and uncontrolled among 32 (53.6%) cases. Of the 18 subjects with controlled diabetes 7 (38.9%) had normal ICA/CCA flow velocity and 7 (38.9%) mild and 4 (22.2%) moderate atherosclerotic disease. Of the 32 patients with uncontrolled diabetes mellitus 2 (6.3%) had normal ICA/CCA flow velocity and 19 (59.4%), 8 (25%) and 3 (9.4%) had mild, moderate and severe atherosclerotic disease respectively (p=0.02) (Table 5).

Table-I

Male female distribution of the study subjects (n=50)

ICA/CCA flow velocity ratio	Gender		P value
	Male	Female	
Normal	3 (6.0%)	6 (12.0%)	0.37
Mild (<2)	17 (34.0%)	9 (18.0%)	
Moderate (2-4)	6 (12.0%)	6 (12.0%)	
Severe (>4)	2 (4.0%)	1 (2.0%)	
Total	28 (56.0%)	22 (44.0%)	

Results were expressed as number (percent).
Chi-square test was performed to calculate statistical association. P value <0.05 was taken as level of significance.

Table-II

Distribution of study subjects on the basis of ICA/CCA flow velocity and age of the subgroups (n=50)

ICA/CCA flow velocity ratio	No (%)	Age (yrs)	p value
Normal	9 (18%)	48.00±4.44	
Mild (<2)	26 (52%)	56.31±4.36	<0.001
Moderate (2-4)	12 (24%)	58.50±8.47	
Severe (>4)	3 (6%)	47.67±2.08	

Results were expressed mean±SD and number (percent) where appropriate. One way ANOVA test was performed to calculate significant association. P value <0.05 was taken as level of significance.

Table-III

Serum triglyceride, total cholesterol and LDL-cholesterol of the study subjects (n=50)

ICA/CCA flow velocity ratio	Triglyceride (mg/dl)	Total cholesterol (mg/dl)	LDL-c (mg/dl)
Normal (n=9)	163±10	176±14	105±21
Mild (<2) (n=26)	196±59	233±13	109±14
Moderate (2-4) (n=12)	217±52	275±15	144±10
Severe (>4) (n=3)	175±13	296±12	157±6
P value	*0.12*	*< 0.001*	*< 0.001*

Results were expressed as mean±SD. One way ANOVA test was performed to calculate significant association. P value <0.05 was taken as level of significance.

Table-IV

Distribution of the study subjects on the basis of ICA/CCA flow velocity ratio and blood pressure (n=50)

ICA/CCA flow velocity ratio	Blood pressure		P value
	Controlled (17)	Uncontrolled (33)	
Normal (n=9)	8 (16.0%)	1 (2.0%)	0.001
Mild (<2) (n=26)	6 (12.0%)	20 (40.0%)	
Moderate (2-4) (n=12)	3 (6.0%)	9 (18.0%)	
Severe (>4) (n=3)	0	3 (6.0%)	

Data were expressed as number percent). Chi-square test was performed to calculate statistical association. P value <0.05 was taken as level of significance.

Table-V

Distribution of the study subjects on the basis of ICA/CCA flow velocity ratio and diabetes control (n=50)

ICA/CCA flow velocity ratio	Diabetes		P value
	Controlled (18)	Uncontrolled (32)	
Normal (n=9)	7 (14%)	2 (4%)	
Mild (<2) (n=16)	7 (14%)	19 (38%)	0.02
Moderate (2-4) (n=12)	4 (8%)	8 (16%)	
Severe (>4) (n=3)	0	3 (6%)	

Data were expressed as number percent). Chi-square test was performed to calculate statistical association. P value <0.05 was taken as level of significance.

Discussion:

Gender bias found to exist in the prevalence of atherosclerotic lesions in the extracranial carotid artery; 4.4% of all the subjects, 7.9% of the men, and 1.3% of the women had atherosclerosis accompanied by stenosis of >50% were found. A strong association between these lesions and the results of a 75g oral glucose tolerance test was found in both sexes[9-12]. Though in other study male gender was found as an independent predictor of carotid atherosclerosis and female gender was found protective[13]. However, no statistical difference was observed regarding frequency of ischemic stroke in the present study.

Among 50 study subjects 82% of the subjects with stroke had mild to severe form of atherosclerosis and 18% had normal flow velocity. The degree of stenosis has been recognized as an important risk factor of stroke[14].

The study showed that in case of mild atherosclerotic disease 12% patient had controlled and 40% uncontrolled HTN In case of moderate atherosclerotic disease 6% patients show controlled HTN, 18% uncontrolled HTN. In case of severe atherosclerotic disease none of the patients had controlled blood pressure. In case of subjects with normal flow ratio 16% had controlled and 2% uncontrolled blood pressure. In case of mild atherosclerotic disease 14% had controlled and 38% uncontrolled DM. In case of moderate atherosclerotic disease 8% patients show controlled DM, 16% patients show uncontrolled DM. In case of severe atherosclerotic disease 0% patient show controlled DM, 6% patient uncontrolled DM. In case of subjects with normal flow ratio 14 % had controlled DM, 4% patients show uncontrolled DM.

Total cholesterol and LDL- cholesterol were found to be associated with degree of stenosis. Similar trend was found with uncontrolled blood pressure and diabetes. Our findings are consistent with literature on risk factors associated with carotid stenosis[15]. Higher prevalence of carotid

atherosclerosis in diabetic subjects compared with non diabetic subjects was shown by other investigators[16].

Increased carotid intimal-medial thickness (IMT) is associated with cardiovascular risk factors and is predictive of stroke in older adults. In men, LDL cholesterol, HDL-cholesterol and diastolic blood pressure were predictive of carotid IMT in a risk factor load model, whereas in women, LDL cholesterol, body mass index, and triglycerides were predictive[17-21].

Intervention trials demonstrated that correction of risk factors, like TG, LDL-c and HDL-c, results in a reduced risk of stroke, at least ishaemic stroke in patients with established IHD. Low levels of HDL-c are common among patients after an ischemic stroke, especially in those with a higher degree of carotid stenosis[22-25]. Multiple regression analysis revealed that carotid atherosclerosis had significant relationships with age, systolic blood pressure, fasting blood glucose, pack-years of smoking, total serum cholesterol, and HDL cholesterol in men ($p<0.05$) and with age, systolic blood pressure, pack-years of smoking, and total serum cholesterol in women ($p<0.05$). Cardiovascular risk factors were strongly related to carotid atherosclerosis and that the proportion of severe carotid atherosclerosis with >50% stenosis was not low and was almost equal to that reported in developed western countries[9-12].

Interesting finding of the present study is that relatively younger subjects suffering from severe carotid atherosclerotic disease as observed by severe restriction of ICA/CCA flow velocity ratio. These subjects are also found to have higher mean total cholesterol and LDL cholesterol level. These later scenario however reconfirm that lipid abnormalities plays an important role in the pathogenesis of atherosclerosis. This study also demonstrated that uncontrolled diabetes mellitus and blood pressure putting additional risks in the vascular pathological process. It is understood that environmental factors play crucial role in the pathogenesis of atherosclerotic disease in the presence of genetic susceptibility. It has also been shown that good metabolic control can prevent or at least delay the atherosclerotic process not only among diabetic but also of the non diabetic subjects.

Routine health check is not practiced in our country. Diabetic patient with ischemic stroke having severely restricted ICA/CCA flow velocity ratio are relatively young. The pathological process, however, suggested to be started much earlier. A regular follow up would have identified the individuals at risk and appropriate measures might have helped in delaying the ongoing process providing them better quality of life. The notable limitation of the present study is the lack of data regarding socioeconomic status which could have assisted in explaining their lifestyle, food habit and above all the socioeconomic transformation.

Conclusion:

Ischemic stroke patients with diabetes have carotid atherosclerosis and they have significant relationship with lipid abnormality. High total cholesterol and LDL cholesterol are associated with degree of carotid atherosclerosis. Study subjects with severe atherosclerotic changes are relatively younger, awareness about the risk factors may help susceptible individuals to modify lifestyle and take medication to prevent or at least delay the events. In the management and investigation plan carotid duplex study should be planned which will identify the individual at risk and suggest them necessary prevention program.

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CASE REPORTS

Hypoglycaemic Brain Injury: A Case Report

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Abstract:

Neurological features of severe hypoglycemia range from reversible focal deficits to irreversible coma or death. Diffusion weighted MRI of brain image is a useful tool in evaluating profound hypoglycemic brain injuries. We report a case of 27 year old male who died from brain injuries following an episode of prolonged hypoglycemia. We here discuss the neuropathological and diffusion-MRI changes of hypoglycemic brain injuries and its prognostic importance.

Keywords: *Hypoglycemia, Brain Injuries, Diffusion Magnetic Resonance Imaging, Cerebral Cortical Necrosis, Prognosis.*

Introduction:

Hypoglycemic brain injury presents with diverse neurological manifestation ranging from reversible brain injury to profound brain damage resulting in death. Out of many radiological sequence of Magnetic Resonance Imaging of brain, Diffusion weighted image is a unique brain image for diagnosing hypoglycemia as well as differentiating it from hypoxic brain injury and also to predict outcome depending on the severity of brain damage. We here report a case of profound hypoglycemic brain injury as evidenced by neuroradiological findings.

Case Report:

A young boy of 17 year old , was admitted in the Intensive Care Unit (ICU) of Square Hospital LTD through Emergency on 5th April of 2012 after being transferred from another hospital with the complaints of decreased level of consciousness for 12 hours, fever and shortness of breath for the same duration and history of multiple drug ingestion 24 hours prior to admission. He was a known case of Yaba and Intravenous drug abuser for last 8 months. According to his parents he took multiple drugs, used by his mother (which included gliclazide, metformin and antihypertensive) for deliberate self harm following a familial conflict one day before admission. Apart from drug abuse he had no known medical illness. He was an A- level student and was the only child of his parents.

On arrival, the patient's physical exam was unremarkable except for his neurological examination. His Glasgow Coma Scale was 7 (E1 V1 M5), his pupils were constricted, round, and non reactive to light and there were no corneal reflexes and Doll's eye reflexes were present. There was decreased tone throughout all four extremities. Neck rigidity and Kernig's sign were negative. Blood pressure was 120/80 mmHg, pulse 75 beats/min, respiratory rate 20 breaths/min, and temperature 102F. The blood glucose was found to be 1.6 mmol/ , which lead to immediate administration of 10% glucose with a bolus followed by continuous infusion. On Baseline Arterial Blood Gas analysis report his arterial pH was 7.402, $Pa0_2$ 51.3 mmHg, $PaC0_2$ 30.1 mmHg, base excess-0.9 mmol/L, and oxygen saturation 88.7%. He was intubated and mechanical ventilation commenced. S. Electrolytes

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were normal. Other blood chemistry results (including Calcium, SGOT, SGPT, Albumin, ALP, Trop I, Gamma GT, PT, aPTT, S. Creatinine, Blood Urea) were unremarkable except for Magnesium(1.2 reference range 1.7- 2.4 mg/dl, CK-MB (68 U/L ref <16), CPK (587 U/L, reference rage: 55-170 for male). His Hb% was 14.1 g/dl and total count of WBC was 25.7 K/mL, neutrophil count 92.7%. Toxicology screening was negative for opiate, amphetamine, barbiturates but benzodiazepine was at upper limit of the normal. Blood and Urine, sputum culture revealed no growth. Viral screening including Hepatitis B, C, HIV, and Herpes were negative. Computed tomography scans showed no findings of acute cerebrovascular injury except for diffuse cerebral and brainstem edema. MRI brain revealed on day 2 showed hyper-intense lesions along the cortices of both cerebral hemispheres signifying restricted diffusion on DW1, while on FSET2 and T2 FLAIR images of the same areas also showed hyperintensities. Similar signal intensities were noted in the right basal ganglia and both thalami with resultant mass effect causing mild ventricular effacement including lateral and 4th ventricle. Adjacent sulcal effacement, mild cerebellar tonsillar herniation and compression over brain stem were also noted. On T2 flair image hyperintensities are noted along the frontoparietal subarachnoid space on both sides, may be due to supplemental oxygen. He was put on intravenous acyclovir empirically as a case of Acute Viral Encephalitis and intravenous broad spectrum antibiotic to cover possible sepsis. He was also treated with intravenous Mannitol to treat brain edema. Despite intensive medical treatment in ICU, the patient's neurological condition failed to improve. The patient died of cardio- respiratory failure on day 11. Postmortem examination was not followed.

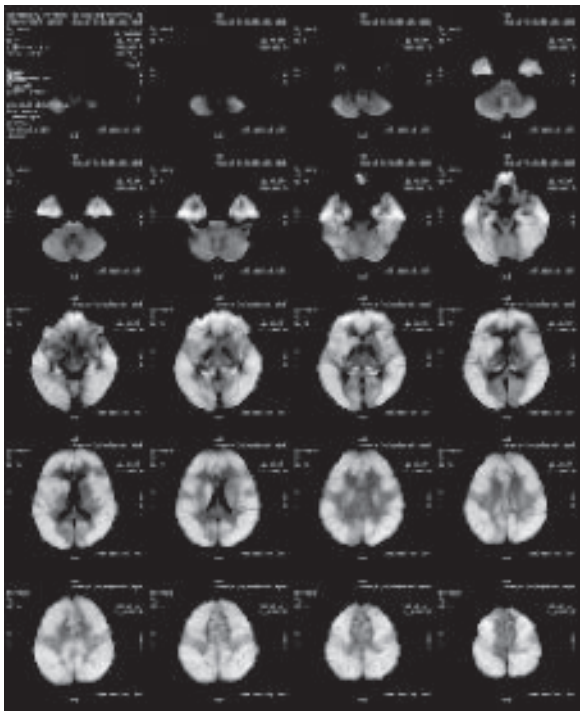

Fig.-1:

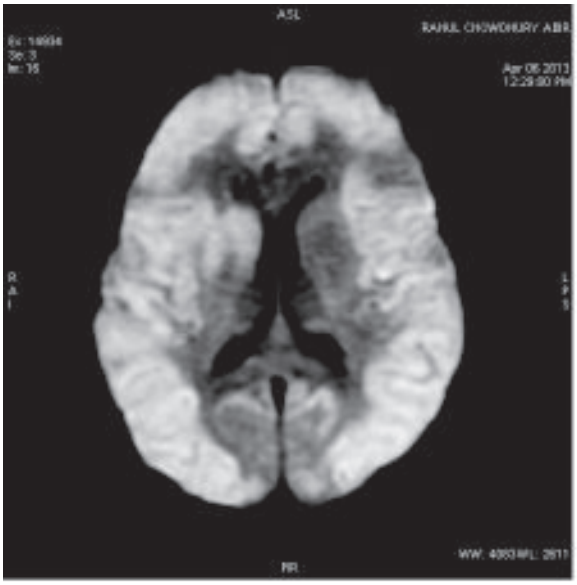

Fig.-2:

Discussion and literature review:

Hypoglycemia is the sudden decrease in serum glucose level <50 mg/dL, and the organ systems that manifest the signs and symptoms are the central and autonomic nervous system.[1] Diverse neurologic manifestations of hypoglycemia have been reported frequently. These neurologic symptoms range from reversible focal neurologic deficits, profound memory loss, transient motor deficits, to permanent dysfunction, persistent vegetative state or death in 2-4%[1-3]. Hypoglycemia can be induced by overuse of insulin or oral hypoglycemic agents, undiagnosed insulinoma, or other medical diseases such as sepsis, or renal, or hepatic failure[1].

Among different brain image sequences Diffusion weighted image (DWI) of Magnetic Resonance Image of brain is a special technique that can measure the alteration of the diffusion of water within the extracellular space and between intracellular and extracellular spaces. These diffusion alterations are encountered not only in acute ischaemia but also in hypoglycemia itself[1]. The commonly affected sites in severe hypoglycemia are Cerebral cortex, Hippocampus, and Basal Ganglia as demonstrated in Neuropathlogical studies; however, the cerebellum and brain stem are usually spared. High-intensity signals are also noted in numerous different locations of the brain like the internal capsules, pons, splenium of the corpus callosum, corona radiata, and cortex of the frontal or parietal or occipital lobe in Diffusion weighted image of patients with acute hypoglycemia[1,2,4].

The pathogenesis of hypoglycemic brain injury still remains unclear. Some proposed pathogenesis for diffusion restriction in hypoglycemic encephalopathy includes the following: 1) energy failure, 2) excitotoxic edema, and 3) asymmetric cerebral blood flow. Neurochemical changes are induced by hypoglycemia. Glucose deprivation leads to arrest of protein synthesis in many regions, incomplete energy failure and loss of ion homeostasis, cellular calcium influx, and intracellular alkalosis. Consequently, neuroactive amino acid (aspartate) release into the extracellular space occurs and results in selective neuronal necrosis, predominantly in the cerebral cortex, caudoputamen, and hippocampus[1]. However, protein synthesis in the cerebellum, brain stem, and hypothalamus remains unaffected because of the greater activity of the glucose transport mechanisms. Excitotoxic edema is a cytotoxic form due to increased extracellular glutamate. The presence of glutamate leads to calcium and sodium entry into the cell and induces apoptosis. In contrast to cytotoxic edema, excitotoxic edema does not imply neuronal damage, because glutamate induces edema of glial cells and myelinic sheaths might protect axons from intracellular edema and irreversible damage. In addition, glutamate reuptake systems are not impaired in hypoglycemia. When hypoperfusion complicates hypoglycemia, the brain is not exposed to an equal fall in perfusion. Due to the focal loss of autoregulation, the frontal and parietal lobe areas have grossly decreased cerebral flow, whereas the cerebellum and brain stem show almost no fall in local cerebral blood flow[1,5-9].

Hypoglycemia constitutes a unique metabolic brain insult. Hypoglycemic effects on the brain are derived mostly from animal studies. Although infarction and hypoglycemia exhibit similar findings on Diffusion weighted image, profound differences are revealed by the neurochemical analyses. Cellular redox system are reduced in ischemia but are oxidized in hypoglycemia, brain pH is decreased in ischemia due to the formation of lactic acid, it is increased in hypoglycemia due to the formation of ammonia from deamination of amino acids, the absence of lactic acid, and the consumption of metabolic acid. In hypoglycemia, adenosine triphosphate levels are still more than one-third of normal but less than 5% in ischemia[10]. Energy failure is considerably less severe in hypoglycaemia than in ischemia as production of lactic acid during hypoglycaemia is not possible due to glucose deficiency[4,5,6,10].If prevailing symmetric superficial laminar necrosis of the cerebral cortex is demonstrable, then hypoglycemic brain damage is more likely, while symmetric superficial laminar necrosis after ischemia is less often seen[4]. Furthermore, hypoglycemia is generalized but not dependent on vascular territories, resulting in a distribution of lesions that does not follow any vascular territory[4].

Post–cardiac arrest encephalopathy share similar findings with hypoglycaemic encephalopathies. Two major differences between hypoglycemic and ischemic encephalopathies have been proposed in one study: (1) serial MR images showed minor hemorrhages in the localized lesions of ischemic encephalopathy but not of hypoglycemic encephalopathy, possibly from tissue acidosis leading to alterations of cerebrovascular permeability and (2) symmetrical thalamic lesions of abnormal intensity on CT and MR images exist in post–cardiac arrest encephalopathy but seem absent in hypoglycemic encephalopathy[11].

Diffusion restricted image of MRI of brain is also valuable in predicting outcome. Several literature reports that reversibility of hyper-intense lesion in diffusion-MRI indicates the good prognosis [2], whereas involvement of the basal ganglia and diffuse and extensive injury predicts a poor neurologic outcome in patients with hypoglycemic injuries[2, 11,13]. MR imaging in our patients showed involvement showed hyper-intense lesions along the cortices of both cerebral hemisphere signifying restricted diffusion on DW1 , while on FSET2 and T2 FLAIR images the same areas also show hyperintensities. Similar signal intensities are noted in the right basal ganglia and both thalami. Resultant mass effect is causing mild ventricular effacement including lateral and 4th ventricle. Adjacent sulcal effacement, mild cerebellar tonsillar herniation and compression over brain stem are also noted. On T2 flair image hyperintensities are noted along the frontoparietal subarachnoid space on both sides, may be due to supplemental oxygen. Our patient had involvement of the cortex, and all cortical lesions were located in the frontal and parietal lobes. The MR imaging findings of our patient were in accord with the proposed mechanisms.

Conclusion:

In hypoglycemic brain injuries neurological deficits and radiologic images are variable. Diffusion weighted image of MRI of brain is a neuroimaging technique that can not only diagnose a case of hypoglycemia but also predicts the outcome and differentiate it from hypoxic brain injury by the characteristic findings of hypoglycemic brain injury. So in case of a suspected hypoglycemic brain injury a Diffusion weighted image of MRI of brain should be requested to see the severity of brain damage as well as to exclude hypoxic ischemic encephalopathy and also to predict outcome.

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The Relationship between Risk Factors and Microalbumiuria for Ischemic Stroke- A Case Control Study

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Abstract:

Background: *Epidemiologic studies have reported that microalbuminuria is a risk factor for stroke in men and a limited case control study found that the highest quintile of microalbuminuria values was associated with 13 fold increased risk for stroke. The goal of this study was designed to determine its relationship to risk factors for ischemic stroke. Materials and* ***Methods:*** *It was a prospective observational study conducted in the Department of Neurology, Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh. Fifty consecutive patients with ischemic stroke were enrolled in this study, with at least two risk factors that fulfilled the inclusion criteria and were confirmed by CT or MRI of brain. Equal number of controls of same age group without stroke who had at least two risk factors was compared with the case group. The patients were assessed clinically with structured questionnaire including blood pressure, height and weight, and monitoring blood glucose and microalbuminuria.* ***Results:*** *Microalbuminuria was found 58.0% in patients with ischemic stroke. Patients who had diabetes mellitus will have 13.86 times the risk for developing of microalbuminuria (p<0.05). Patients who had hypertension will have 4.19 times the risk of developing microalbuminuria (p<0.05) and BMI (e"23 kg/m^2) will have 4.24 times the risk of developing microalbuminuria (p<0.05). Whereas TIA, IHD, dyslipidemia, smoking and positive family history were not significantly (P>0.05) associated with microalbuminuria in patients with ischemic stroke.* ***Conclusion:*** *The findings of this study show that diabetes is the factor most closely associated with microalbuminuria followed by HTN and BMI >23 kg/ m^2 with statistically significance in patients with ischemic stroke.*

Keywords: *Microalbuminuria, risk factors, Ischemic stroke*

Abbreviation: *TIA (transient ischemic stroke), HTN (hypertension), BMI (basal metabolic index), IHD(ischemic heart disease)*

Introduction:

Stroke is a neurological disease, which is a major cause of death and disability worldwide. Stroke kills about five million people each year making this the second major cause of death worldwide. At least fifteen million others have non-fatal stroke annually and about a third are disabled as a consequence[1]. The word stroke is used to refer to a clinical syndrome, of presumed vascular origin, typified by rapidly developing signs of focal or global disturbance of cerebral functions lasting more than 24 hours or leading to death[2]. Among Risk factors for stroke advance age, male sex , hypertension, previous stroke or transient ischemic attack (TIA), diabetes mellitus, high cholesterol, smoking, and mitral valvular heart disease with atrial fibrillation

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are well established in ischemic stroke[3]. Microalbuminuria is commonly thought of as an important risk factor for kidney disease, but recently studies have emerged highlighting microalbuminuria as an important, independent marker for endothelial dysfunction and ischemic stroke. Increasing the awareness of microalbuminuria as an early prognostic indicator of stroke risk[4-8].

Microalbuminuria is the excretion of greater than 30 mg and less than 300 mg a day of albumin in the urine. The normal urinary albumin is less than 30 mg per 24 hours[9]. Nephrologists and diabetologist measure microalbuminuria to monitor the development and progression of kidney disease, but now studies have shown a clear relationship between microalbuminuria and cardiovascular events[10].Microalbuminuria is present in a section of population known to be risk for stroke, including people with type 1, type 2 diabetes, hypertension, endothelial dysfunction, and other feature of insulin resistance. The prevalence of microalbuminuria 20-40% in diabetes, 40% of poorly controlled hypertensive individual have microablbuminuria and that its prevalence increases with duration and severity of hypertention[4,5]. Hypertensive patients also have microalbuminuria more frequently have left ventricular hypertrophy, carotid artery thickening and other end organ damage[6].

Microalbuminuria can also predict a deleterious cardiovascular prognosis in other individual, such as patient with dyslipidemia or the cluster of risk factors like metabolic syndrome, abdominal obesity, elevated triglycerides, and elevated fasting blood glucose[5].

Although studies have shown that small increase in urinary excretion of albumin predict adverse renal and vascular events in patient with diabetes, hypertension, or both. But the exact mechanism particularly in stroke is unknown. Many researchers have hypothesized that microalbuminuria is associated with generalized endothelial dysfunction[4].

The current consensus among researcher is that albumin passes through the vascular wall, and this increased permeability is a marker of endothelial dysfunction. In diabetic and hypertensive patient with microalbuminuria have shown that increase albumin leakage in the glomerulus is linked to enhance capillary permeability for albumin in the systemic vasculature[4].

Researcher hypothesized that such leakage leads to hemodynamic strain and instability, which starts the atherosclerotic process, and eventually lead to adverse vascular event like Ischemic stroke [7].Although microalbuminuria is associated with clinical risk factor for stroke, there is surprisingly little information regarding it as an independent risk factor for stroke or a predictor of stroke outcome. A large prospective study has reported that microalbuminuria is a risk factor for stroke in men and a limited case control study found that the highest quintile of microalbuminuria values was associated with 13 fold increased risk for stroke[9].

Materials and Methods:

This prospective observational case-control study of microalbuminuria as risk factor for acute ischemic stroke was conducted for 50 consecutive male and female patients who were admitted in the Department of Neurology and Medicine of Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh from July 2011 to June 2012 (1 year). Criteria for inclusion in this study were :(1). First ever acute ischemic stroke,(2). CT scan or MRI suggestive for ischemic stroke, (3). Who have at least 2 risk factors like male, family history, diabetes mellitus(DM), dyslipidemia, transient ischemic attack (TIA), cigarette smoking, hypertension, high Body Mass Index (BMI) and (4). age >25 years. The patients age and sex match with the cases who fulfilled the criteria for at least 2 risk factors as male, family history, DM, dyslipidemia, TIA, cigarette smoking, hypertension, high BMI without stroke will be considered as control.

Clinical information including age, sex, history or current evidence of hypertension (HTN) [systolic blood pressure (SBP) >150mmHg and diastolic BP >90mmHg], diabetes mellitus (DM), cardiac disease, were recorded for all subjects. Plasma glucose (Fasting, 2 hours after breakfast, Random blood glucose, Glycosylated hemoglobin A1c

(HbA1c), fasting lipid profile(Minimum 8 hours fasting), first morning void urine sample for microalbumin estimation. Plasma glucose and cholesterol levels were measured with an Express 550 clinical chemistry autoanalyzer (Ciba Corning Diagnostic Corp) in fasting conditions of 8 to 10 hours. HbA1c percentage was measured by HPLC, and the normal range was 4.5% to 6.5%.Microalbuminuria was tested by Micral test (Roche diagnostic manufacturer, Ltd). This test was also based on the color shift of a monoclonal antibody to human albumin after binding of urinary albumin to antibody. It was a semi-quantitative screening tool and the results of this test were read as 0 mg/L, 20 mg/L, 50mg/L and 100 mg/L. A reading of 20 mg/L or more was considered positive, according to manufacturer's recommendation. Data were collected by a predesigned proforma. Patient's information was obtained through using patient's information sheet which involves questionnaire, clinical findings, and biochemical findings, CT scan / MRI of brain and Duplex study of the neck vessels, Echocardiogram. All the cases and controls were informed about the nature of the study. Their informed written consent was taken in a consent form before collecting data. Proper permission was taken from the concerned departments and local ethical committee.

Statistical analyses related with this study were performed by use of SPSS 16.0 package program. The data was expressed by descriptive statistical methods like average, frequency distribution, percentage, mean & standard deviation as applicable. Comparison between groups was done by standard statistical test e.g. Chi-square test or other tests as applicable. Relationship between risk factor and microalbuminuria in ischemic stroke were investigated by odds ratio.

Results:

Mean age was found 57.96±12.83 years in group I and 54.71±11.7 years in group II. Mean difference was statistically non significant (P>0.05) between two groups.

Males were predominant of the both groups, which was 28 cases(56.0%) in group I and 26 cases(52.0%) in group II. The difference was not statistically significant (P>0.05) between two groups.

The mean BMI was found 22.47±4.68 kg/m^2 in group I and 23.35±4.72 kg/m^2 in group II. The mean difference was not statistically significant (P>0.05) between two groups. BMIe"23 was found 15 (30%) in group I and 24(48%) in group II

H/O of TIA was found 4(8.0%) in group I and 2(4.0%) in group II. HTN was found in 31(62.0%) and 40(80.0%) group I and group II respectively. DM was 19(38.0%) in group I and 28(56.0%) in group II.. Dyslipidaemia was 15(30.0%) in group I and 26(52.0%) in group II. Family history was found in 26(52.0%) and 38(76.0%) in group I and group II respectively. Smoker was 20(40.0%) in group I and 13(26.0%) in group II. Drug history (HTN, DM, dyslipidaemia) was found in 30(60.0%) in group I and 21(42.0%) in group II. BMI (e"23 kg/m^2) was found 15(30.0%) in group I and 24(48.0%) in group II. HTN, dyslipidemia and family history difference was statistically significant (P<0.05) between two groups.

Table-I

Age distribution of the study patients (n=100)

Age (in years)	Group I(n=50)		Group II(n=50)		P value
	n	%	n	%	
d"30	1	2.0	1	2.0	
31-40	2	4.0	6	12.0	
41-50	12	24.0	21	42.0	
51-60	15	30.0	14	28.0	
61-70	8	16.0	5	10.0	
71-80	11	22.0	2	4.0	
>80	1	2.0	1	2.0	
Mean ± SD	57.96±12.83		54.71±11.7		0.187^{ns}
Range (min-max)	(25-85)		(30-90)		

Group I: Case & Group II: Control. s=significant, P value reached from unpaired t-test.

Table-II

Sex distribution of the study patients (n=100)

Sex	Group I(n=50)		Group II(n=50)		P value
	n	%	n	%	
Male	28	56.0	26	52.0	0.688^{ns}
Female	22	44.0	24	48.0	

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

Table-III

Distribution of the study patients according to body mass index (BMI) (n=100)

BMI (kg/m^2)	Group I(n=50)		Group II(n=50)		P value
	n	%	n	%	
<18.5	9	18.0	3	6.0	
18.5-23	26	52.0	23	46.0	
23-27.5	12	24.0	17	34.0	
e”27.5	3	6.0	7	14.0	
Mean±SD	22.47±4.68		23.35±4.72		0.351^{ns}
Range (min-max)	(15-36.16)		(14.86-36.5)		

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

Table-IV

Distribution of the study patients according to risk factors (n=100)

Risk factors	Group I(n=50)		Group II(n=50)		P value
	n	%	n	%	
H/O TIA					
Yes	4	8.0	2	4.0	0.338^{ns}
No	46	92.0	48	96.0	
HTN					
Yes	31	62.0	40	80.0	0.047^{s}
No	19	38.0	10	20.0	
DM					
Yes	19	38.0	28	56.0	0.071^{ns}
No	31	62.0	22	44.0	
Dyslipidemia					
Yes	15	30.0	26	52.0	0.025^{s}
No	35	70.0	24	48.0	
Family history					
Yes	26	52.0	38	76.0	0.012^{s}
No	24	48.0	12	24.0	
Smoking					
Yes	20	40.0	13	26.0	0.136^{ns}
No	30	60.0	37	74.0	
Drug history (HTN, DM, Dyslipidaemia)					
Yes	30	60.0	21	42.0	0.071^{ns}
No	20	40.0	29	58.0	
BMI (e”23 kg/m^2)					
Yes	15	30.0	24	48.0	0.065^{ns}
No	35	70.0	26	52.0	

s=significant; ns=not significant, P value reached from chi square test.

Mean systolic BP was found 142.5±27.26 mmHg in group I and 136.22±33.7 mmHg in group II. Mean diastolic BP was found 85.8±14.01 mmHg and 81.71±16.72 mmHg in group I and group II respectively. The difference was not statistically significant (P>0.05) between two groups.

The mean fasting blood sugar was found 9.71±4.32 in group I and 6.59±1.06 in group II. The mean random blood sugar was found 9.0±4.36 and 9.84±5.2 in group I and group II respectively. Mean fasting blood sugar difference was statistically significant (P<0.05) between two groups but not in random sugar groups.

Mean HbA_1C was found 9.04±4.26% in group I and 7.02±2.05% in group II. The difference was statistically significant (P<0.05) between two groups.

Positive microalbuminuria was found 29(58.0%) in group I and 16(32.0%) in group II. Negative microalbuminuria was 21(42.0%)in group I and 34(68.0%) group II. The difference was statistically significant (P<0.05) between two groups.

Patients with microalbuminuria (in case group), 3(10.3%) had TIA, 22(75.9%) had HTN, 17(58.6%) had DM, 4(13.8%) had IHD, 7(24.1%) had dyslipidemia, 10(34.5%) had smoking, 18(62.1%) had family history and 12(41.4%) had BMI (e"23 kg/m^2)

Patients without microalbuminuria (in case group), 1(4.8%) had TIA, 9(42.9%) HTN, 2(9.5%) DM, 1(4.8%) IHD, 8(38.1%) dyslipidemia, 10(47.6%) smoking, 8(38.1%) family history and 3(14.3%) BMI (<23 kg/m^2).

The patients who had DM will have risk of microalbuminuria is 13.86 times of the patients who did not, but it has statistically significant (95% CI 2.29%-92.64%); p value<0.05).

The patients who had HTN wil have risk of microalbuminuria is 4.19 times of the patients who did not, but it has statistically significant (95% CI 1.07%-17.11%); p value <0.05).

The patients who had BMI (>23 kg/m^2) will have risk of microalbuminuria is 4.24 times more of the patients who did not, but it has statistically significant (95% CI 0.87%-23.06%); p value<0.05).

The patients who had TIA will have risk of microalbuminuria is 2.31 times more of the patients who did not have TIA. It is not statistically significant (95% CI 0.19%-62.29%); p value>0.05).

The patients who had dyslipidemia will have risk of microalbuminuria is 0.52 times more of the patients who did not, but it has no statistic significance (95% CI 0.13%-2.07%); p value>0.05).

The patients who had smoking will have risk of microalbuminuria is 0.58 times more of the patients who did not, but it has no statistic significance (95% CI 0.16%-2.12%); p value>0.05).

The patients who had family history will have risk of microalbuminuria is 2.66 times more of the patients who did not, but it has no statistical significance (95% CI 0.72%-10.04%); p value>0.05).

Patient having positive microalbuminuria 3.84(95% CI 1.4% to 10.55%) times more likely to have stroke. On the other hand patient having DM 2.17(95% CI 1.22% to 8.03%) times more likely to have stroke and patient having HTN 1.92(95% CI 1.30% to 7.83%) times more likely to have stroke. Other risk factors were not significantly (P>0.05) associated with stroke in multivariate analysis.

Table V

Distribution of the study patients according to blood pressure (n=100)

Blood Pressure (mmHg)	Group I(n=50) Mean± SD	Group II(n=50) Mean± SD	P value
Systolic	142.5±27.26	136.22±33.7	0.308^{ns}
Range (min-max)	(90-210)	(90-240)	
Diastolic	85.8±14.01	81.71±16.72	0.188^{ns}
Range (min-max)	(50-120)	(50-140)	

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

Table-VI

Distribution of the study patients according to fasting blood sugar and random blood sugar (n=100)

	Group I(n=50) Mean±SD	Group II(n=50) Mean± SD	P value
Fasting blood sugar	9.71±4.32	6.59±1.06	0.001[s]
Range (min-max)	(5.4-17)	(5-8.1)	
Random blood sugar	9.0±4.36	9.84±5.2	0.383[ns]
Range (min-max)	(5.2-21)	(5-25)	

s=significant; ns=not significant. P value reached from unpaired t-test.

Table VII

Distribution of the study patients according to HbA_1C (n=100)

	Group I(n=50) Mean± SD	Group II(n=50) Mean± SD	P value
HbA_1C	9.04±4.26	7.02±2.05	0.003[s]
Range (min-max)	(5.4-16.87)	(5.07-11.7)	

s=significant, P value reached from unpaired t-test.

Table-VIII

Distribution of the study patients according to microalbuminuria (n=100)

Microalbuminuria	Group I(n=50)		Group II(n=50)		P value
	n	%	n	%	
Positive (30-299 mg/24h)	29	58.0	16	32.0	0.008[s]
Negative (<30 mg/24h)	21	42.0	34	68.0	

s=significant .P value reached from chi square test.

Table-IX

Relationship of risk factors with microalbuminuria for ischemic stroke patients (n=50).

Risk factors	Microalbuminuria				OR (95% CI)	P value
	Yes(n=29)		No(n =21)			
	n	%	n	%		
DM	17	58.6	2	9.5	13.86(2.29-92.64)	0.001[s]
HTN	22	75.9	9	42.9	4.19(1.07-17.11)	0.018[s]
BMI (e"23 kg/m^2)	12	41.4	3	14.3	4.24(0.87-23.06)	0.039[s]
TIA	3	10.3	1	4.8	2.31(0.19-62.29)	0.436[ns]
Dyslipidemia	7	24.1	8	38.1	0.52(0.13-2.07)	0.287[ns]
Smoking	10	34.5	10	47.6	0.58(0.16-2.12)	0.349[ns]
Family history	18	62.1	8	38.1	2.66(0.72-10.04)	0.093[ns]

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

Table-X

Multiple Logistic regression models for risk factors associated with ischemic stroke.

	OR	95.0% CI for OR		P value
		Lower	Upper	
Microalbuminuria	3.84	1.40	10.55	0.009s
DM	2.17	1.22	8.03	0.012s
HTN	1.92	1.30	7.83	0.039s
H/O TIA	0.58	0.28	1.55	0.461ns
Dyslipidemia	0.36	0.14	0.95	0.889ns
Family History	0.26	0.09	0.75	0.279ns
Smoking	1.27	0.44	3.66	0.656ns
BMI(e”23 kg/m²)	0.91	0.34	2.44	0.848ns
Constant	3.51	0.28	17.03	0.101ns

S=significant; ns=not significant

Discussion:

This case control study was carried out with an aim to determine the incidence of microalbuminuria in patients with ischemic stroke and to determine the relationship between the risk factors for ischemic stroke and microalbuminuria .

A total number of 50 consecutive patients having first ever ischemic stroke and 50 patients without ischemic stroke but both had at least two risk factors according to inclusion criteria, were considered as group I and group II respectively. The present study findings were discussed and compared with previously published relevant studies.

In this current study in Table I, it was observed that the mean age was 57.96±12.83 years with range from 25 to 85 years in group I and 54.71±11.7 years with range from 30 to 90 years in group II. The mean difference of age was not statistically significant (P>0.05) between two groups. In a recent study showed the mean age was 66.1±12.7 years with range from 28-90 years in patients having ischemic stroke[9]. In another study, found mean age were 59.1±8.3 years and 59.3±10.4 years in patients having ischemic stroke and without ischemic stroke respectively which is similar with this study[11].

Regarding the sex incidence (Table II), it was observed that male predominant in both groups, which was 56.0% in group I and 52.0% in group II. Male to female ratio was 1.2:1 in the whole study patients. However, the male female difference was not statistically significant (P>0.05) between two groups. Similarly, male predominant also observed in other studies [12, 13]. In another study, it was observed that the male to female ratio was almost 1:2 in their study[11].

In this study (Table III), it was observed that the mean BMI was found 22.47±4.68 kg/m^2 in group I and 23.35±4.72 kg/m^2 in group II, which was almost similar between two groups. No statistical significant (P>0.05) difference was found between two groups. A a recent study, they showed higher mean BMI[12], where the authors found the mean BMI was 27.0±4.3 kg/m^2 and 24.8±3.0 kg/m^2 in group I and group II respectively. A another study, the mean BMI was 27.9±4.1 kg/m^2 in group I and 28.3±4.8 kg/m^2 in group II[14]. In another study it was was observed that the mean BMI was 29.5±3.6 kg/m^2 and 27.2±1.8 kg/m^2 in group I and group II respectively[16]. They have stated that the higher BMI range maybe due to their body surface area in their study patients.

Regarding the risk factors associated with ischemic stroke (Table IV), it was observed that the previous history of TIA was found 8.0% in group I and 4.0% in group II. HTN was found in 62.0% and 80.0% group I and group II respectively. DM was found in 38.0% in group I and 56.0% in group II. Family history was found in 52.0% and 76.0% in group I and group II respectively. Smoker was

40.0% in group I and 26.0% in group II. Drug history (HTN, DM, dyslipidemia) was found in 60.0% in group I and 42.0% in group II. BMI (e"23 kg/m2) was found 30.0% in group I and 48.0% in group II. HTN, dyslipidemia and family history were significantly (P<0.05) higher in group II. In a similar study, hypertension was found in 10.2% and 13.8% in group I and group II respectively, which is less than the current study[11].This may be due to the current study patients mostly came from low socio-economic status and they didn't received any antihypertensive drugs, as they had lack of health education and awareness . The authors also observed diabetes 42.4% in group I and 55.5% in group II. Smoker was found 23.7% in group I and 16.1% in group II, which are almost similar with the current study[9]. In another study, showed that 64.0% and 45.0% were smoker in group I and group II respectively, which was higher than the current study[12].

In this series in Table V, it was observed that the mean systolic BP was found 142.5±27.26 mmHg with range from 90 to 210 mmHg in group I and 136.22±33.7 mmHg with range from 90 to 240 mmHg in group II. Mean diastolic BP was found 85.8±14.01 mmHg with range from 50 to 120 mmHg and 81.71±16.72 mmHg with range from 50 to 140 mmHg in group I and group II respectively. The mean systolic and diastolic BP were higher in group I but not statistically significant (P>0.05) between two groups. Similarly, the higher mean systolic and diastolic BP were also observe[12], where the mean systolic BP was found 173.0±16.0 mmHg and 162.0±8.0 mmHg in group I and group II respectively. Similarly, the mean diastolic BP was found 98.0±8.0 mmHg in group I and 101.0±8 mmHg in group II, which are compatible with the current study. On the other hand, a recent study showed the mean systolic BP was 137±13 mmHg and 128±11 mmHg in group I and group II respectively[15].The mean diastolic BP was 78.6±9.9 mmHg in group I and 75.6±7 mmHg in group II, which are compatible with the current study.

In this current study in Table VI was observed that the mean fasting blood sugar was found 9.71±4.32 mmol/l varied from 5.4 to 17 mmol/l in group I and 6.59±1.06 mmol/l varied from 5.0 to 8.1 mg/dl in group II. Random blood sugar was found 9.0±4.36 mmol/l varied from 5.2 to 21 mmol/l and 9.84±5.2 mmol/l varied from 5.0 to 25 mmol/l in group I and group II respectively. Mean fasting blood sugar was significantly (P<0.05) higher in group I, whereas blood sugar was almost similar between two groups. In another study showed the mean fasting blood sugar was 7.7±2.7 mmol/l in group I and 8.2±2.6 mmol/l in group II[16].

In this present series (Table VII), it was observed that the mean HbA_1C was found 9.04±4.26% with range from 5.4 to 16.87% in group I and 7.02±2.05% with range from 5.07 to 11.7% in group II. The mean HbA_1C was significantly (P<0.05) higher in group I patients. Almost similar findings were observed in a study , where they found the mean HbA_1C was 8.8±1.3% and 7.1 ± 1.5% in group I and group II respectively[16]. In similar studies, it was found that the mean HbA_1C was 7.3±1.3% in group I and 6.5±1.3% in group II[14,1] All these results support the present study.

Recently in a study it was revealed that, in the general population, microalbuminuria had a prognostic significance in patients with stroke, independently predicting recurrent strokes and mortality[18]. In another study, it was observed that microalbuminuria was independently associated with carotid artery intima-media thickness in nondiabetic individuals in the Insulin Resistance and Atherosclerosis Study, USA[19]. Carotid intima-media thickness is a risk factor for stroke and coronary heart disease [20].

In this current study (Table VIII), it was observed that positive microalbuminuria was found 58.0% in group I and 32.0% in group II. Negative microalbuminuria was 42.0% and 68.0% in group I and group II respectively. Positive micro-albuminuria was significantly (P<0.05) higher in patient with ischemic stroke. In another study showed that positive microalbuminuria was 64.0% and 25.0% in group I and group II respectively[12]. Beamer et al. showed microalbuminuria 29.9% in group I and 19.6% in group II patients[13] .The above findings are consistent with the current study.

A total of 50 patients having ischemic stroke, out of which 29(58.0%) and 21(42.0%) patients with

microalbuminuria and without microalbuminuria respectively. In this present study (Table IX), it was observed that in patients having microalbuminuria with ischemic stroke patients that 58.6% had DM, 75.9%had HTN, 41.4% BMI e"23 kg/m^2, 10.3% had TIA, 24.1% dyslipidemia, 34.5% smoker and 62.1% had positive family history. On the other hand, patients without microalbuminuria in patient with ischemic stroke, 9.5% had DM, 42.9% HTN 14.3% had BMI >23 kg/m2, 4.8% had TIA, 38.1% dyslipidaemia, 47.6% smoker and 38.1% had positive family history.

Recent study showed out of 139 hypertensive patients, 23.74% had microalbuminuria and out of 55 diabetic patients, 54.55% had microalbuminuria and out of 98 patients with dyslipidemia, 24.49% had microalbuminuria, which is consistent with the current study[9].

In this present series it was observed that the patients who had diabetes mellitus will have 13.86 times more risk for developing microalbuminuria with 95% CI 2.29%-92.64%; ($p<0.05$). Patients who had HTN will have 4.19 times more the risk for developing microalbuminuria with 95% CI 1.07%-17.11%; ($p<0.05$). Patients who had BMI >23 kg/m^2 will have 4.24 times more risk for developing microalbuminuria with 95% CI 0.87%-23.06%; ($p<0.05$). Whereas TIA, dyslipidemia, smoking and positive family history were not significantly ($P>0.05$) associated with microalbuminuria in patients with ischemic stroke. To determine which factors were independently associated with the risk of stroke, multivariate logistic regression analysis were performed and revealed microalbuminuria, DM, HTN remained as independent predictor for ischemic stroke. This finding showed that patients having positive microalbuminuria had 3.84(95% CI 1.4% to 10.55%) times more likely to have stroke (Table X). On the other hand patient having DM 2.17(95% CI 1.22% to 8.03%) times more likely to have stroke and patient having HTN 1.92(95% CI 1.30% to 7.83%) times more likely to have stroke. Other risk factors were not significantly ($P>0.05$) associated with stroke in multivariate analysis.

A number of prospective studies observed that microalbuminuria predicts a cause of cardiovascular mortality in the general population[21-23]. The EPIC-Norfolk study was the first report evaluating the prospective relationship between microalbuminuria and incidence of fatal and nonfatal cerebrovascular disease in the general population[24].The mechanism of the association between albuminuria and stroke is still largely unknown and a focus of research and debate mentioned[9]. Several explanations have been suggested: Microalbuminuria may reflect universal endothelial dysfunction that might enhance the penetration of atherogenic lipoproteins into the arterial wall [25]. Microalbuminuria is a marker of established CVD[26].Microalbuminuria and cerebrovascular disease are not causally related but rather reflect common determinants[27,28] . So this hospital based observational study, established the relationship between risk factor and microalbuminuria for ischemic stroke.

Conclusion:

This case control observational study showed that diabetes is the factor most closely associated with microalbuminuria followed by HTN and BMI e"23 kg/m^2 with statistically significance in patients with ischemic stroke.

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Seasonal Variations of Aneurismal Subarachnoid Hemorrhage

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***Abstract**:*

***Background:** Rupture of aneurysm is a vascular events, it is assumed that season exerts an influence in the incidence of rupture of aneurysm. But seasonal variation on the aneurismal subarachnoid hemorrhage (ASAH) is a subject of controversy. Some previous studies reported that changes in the biometric pressure in different season modulate the occurrence of vascular events. **Aims**: To evaluate the role of seasons of a year on the onset of aneurismal subarachnoid hemorrhage (ASAH).**Methodology**: This is a retrospective study. There were 377 patients with definite diagnosis of ASAH. Patients were evaluated in two age groups of >60 and less than 60.**Results**: The frequency of ASAH in winter and autumn was 55.4% and spring and summer was 44.6%% respectively. This difference was statistically significant (p>o.o5). The effect of hypertension and diabetes mellitus revealed no influence on subarachnoid hemorrhage (SAH) in our study. **Conclusion**: There was influence of seasonal variation on the onset of ASAH and which was predominantly during winter and autumn.*

***Key words:** Seasonal, variation, aneurysm, subarachnoid hemorrhage*

***Abbreviation**: ASAH –Aneurismal subarachnoid hemorrhage. SAH (subarachnoid hemorrhage) DM – Diabetes Mellitus.*

Introduction:

The seasonal variations in the incidence of hypertension, cerebrovascular accident, coronary heart disease were well reported. But seasonal variation on the aneurismal subarachnoid hemorrhage (ASAH) is a subject of controversy. Some previous studies reported that changes in the biometric pressure in different season modulate the occurrence of vascular events [1-3]. As rupture of aneurysm is also a vascular event, it is assumed that season exerts an influence in the incidence of rupture of aneurysm. It is well reported in some studies that season exerts an influence in the incidence of coronary heart disease, hypertension, cerebrovascular accident [1-3] and even nonvascular disorders such as pancreatitis.

However, the relation between season and onset of SAH was a subject of controversy till now. Some showed that a considerable increase in the occurrence of SAH if there was changes in the blood pressure [4]. In a study on 761 cases of SAH by Hanken *et al.* didn't show any significant difference with blood pressure change [3]. These conflicting results produce a need to design more new studies in this regards. In the present study, we aimed to evaluate if there was any variations of different season of year on the onset of SAH due to rupture of aneurysm.

Material and method:

In a retrospective study, all files of patients from year 2007 to 2010 that fulfilled the criteria for ASAH in Max Hospital, New Delhi were reviewed for appropriate data including age, sex and history of hypertension and DM. The definite diagnoses of SAH recorded from the files with patient's history and clinical findings that were confirmed by computed tomography scan (CT scan). Aneurysm is confirmed by angiographically or typical

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aneusymal blood in CT scan of brain. SAH due to other reasons, such as arteriovenous malformation, trauma, malignancy etc. were excluded from this study. Any history of hypertension or DM reported in the admission note was included. Finally, the patients were evaluated in two age groups of < 60 years and >60 years in relation to the seasonal variation of ASAH. The data will be processed and analyzed by computer software SPSS (Statistical Package for Social Science) version 10. Level of significance will be considered as p value less than 0.05. Chi Square test was used for comparison.

Result:

There were three hundred and seventy seven patients that fulfilled criteria of ASAH. The mean age of 76.4% of patients was < 60 years and for 23.6 % was >60 years. The male to female ratio was 1:1.

Moreover, the frequency of ASAH in summer, spring, winter autumn were 18.3%, 23.6%, 27.0% and 28.4% respectively(Table:I). The frequency of ASAH in winter and autumn was about 55.4% and that of spring and summer was 44.6%. This difference was statistically significant (P < .OO5)

However, according to the age, the seasonal frequency of ASAH was not different between <60 years and >60 years (P = 0.205) and the difference was not statistically significant (Tables II). Also according to the gender (Table III), the seasonal frequency of ASAH was not different between males and females (P = 0.796). Table IV showed that only 3.2% patients were diabetic and rest were nondiabetic which revealed no variation by season. Similarly table V showed that 24.4% of patients were hypertensive and rest were nonhypertensive but there were no seasonal variations. (P< 0.05).

Table-I

Distribution of ASAH by season

Season	Frequency	Percent
Spring	69	18.3
Summer	99	26.3
Autumn	102	27.0
Winter	107	28.4
Total	377	100.0

p value = 0.004, z test was done to measure the level of significant.

The frequency of ASAH in winter and autumn fall was about 55.4% and that of spring and summer was 44.6% and this difference was statistically significant.

Table-II

Distribution of age by seasons

Season	Age (in year)		p value*
	<60 year	>60 year	
Spring	49 (71.0)	20 (29.0)	
Summer	71 (71.7)	28 (28.3)	0.205
Autumn	84 (82.4)	18 (17.6)	
Winter	84 (78.5)	23 (21.5)	
Total	288 (76.4)	89 (23.6)	

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

Table-III

Distribution of sex by seasons

Season	Sex		p value*
	Male	Female	
Spring	32 (46.4)	37 (53.6)	
Summer	53 (53.5)	46 (46.5)	0.796
Autumn	49 (48.0)	53 (52.0)	
Winter	54 (50.5)	53 (49.5)	
Total	188 (49.9)	189 (50.1)	

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

Table-IV

Distribution of DM by seasons

Season	DM		p value*
	Yes	No	
Spring	0 (.0)	69 (100.0)	
Summer	2 (2.0)	97 (98.0)	0.217
Autumn	5 (4.9)	97 (95.1)	
Winter	5 (4.7)	102 (95.3)	
Total	12 (3.2)	365 (96.8)	

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

Table-V

Distribution of HTN by seasons

Season	HTN		p value*
	Yes	No	
Spring	12 (17.4)	57 (82.6)	
Summer	25 (25.3)	74 (74.7)	0.428
Autumn	29 (28.4)	73 (71.6)	
Winter	26 (24.3)	81 (75.7)	
Total	92 (24.4)	285 (75.6)	

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

Discussion:

Seasonal variation of ASAH was a controversy. One study showed a definite seasonal variation of SAH in regions with tropical climate [4]. However, in regions with subtropical weather, this variation remained uncertain[5]. In that manner, in our study undertaken in Max Hospital, New Delhi with variable climate, we also found considerable difference. The rate of incidence was more in winter and autumn but less in summer and spring. On the other hand, the clear role of climate may be difficult to estimate the difference in variation of activities that may trigger the onset of ASAH more strongly than climate [6].

Some previous studies demonstrated the correlation between seasonal variation and onset of SAH in patient's of >60 years old[5-8], but in the present study the difference between patients who were >60 years old or less than 60 years was not significant. Moreover, changes of blood pressures which were cited as a main factor in the onset of ASAH in some studies [8-10]. In this study no significant relation was found between blood pressure changes and rupture of SAH with seasons. Similarly, no significant relation was found among diabetic and nondiabetic patients with seasonal variation with SAH. However, studies of larger sample groups are needed to evaluate the influence of blood pressure and diabetes with rupture of SAH and seasonal variations.

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Association of Ankle Brachial Pressure Index (ABPI) in Patients with Ischemic Stroke: A Case-Control Study

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Abstract:

Background: *Several epidemiological studies have identified the association of abnormal ABPI with ischemic stroke. So the goal of this study was to determine the actual relationship of ABPI with ischemic stroke in the context of our country.* ***Materials and Methods:*** *This case control study was carried out in the Department of Neurology, Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh. ABPI was measured by Doppler ultrasound machine of 100 patients who were admitted to the Mitford Hospital during the study period. Among them 50 patients with Ischemic stroke, confirmed by CT/MRI scan of brain were considered as 'case' and 50 age- sex matched individuals with one or more vascular risk factors (VRF) but without stroke were considered as 'control'. Then the results of ABPI were compared between the two groups.* ***Results:*** *Among the 50 patients with ischemic stroke (case group) , 74% had normal ABPI and 26% had ABPI< 0.9; on the other hand among 50 age and sex matched individuals (control group) 90% had normal ABPI and 10% had ABPI <0.9. The difference was statistically significant between two groups (p=<0.05).This association remained significant even after adjustment for potential confounders (age, gender, high BMI, hypertension, diabetes mellitus, hyperlipidemia, smoking, ischemic heart disease and family history) in a multiple logistic regression model.* ***Conclusion:*** *The incidence of low ABPI is significantly higher in ischemic stroke patients than the age- sex matched control.*

Key words: *Ischemic stroke, Ankle Brachial Pressure Index (ABPI), vascular risk factors (VRF).*

Introduction:

Stroke is a major global health hazard. It is the third leading cause of death after heart disease and cancer, after the age of 40[1]. Annually 15 million people suffer a stroke worldwide. Of these, 5 million die and another 5 million are left permanently disabled, placing a burden on family and community[2].

Stroke is defined as a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal and at times global loss of brain function, with symptoms lasting >24 hours or leading to earlier death, and with no apparent cause other than that of vascular origin[3]. Among the two major types, ischemic stroke comprises 85% while hemorrhagic stroke is only 15%.[4] Both intra- and extra-cranial atherosclerosis play a key role for ischemic stroke[5].

The well established risk factors for ischemic stroke include advanced age, male gender, previous history of stroke, hypertension, diabetes mellitus, obesity, dyslipidemia, cigarette smoking, heart disease, transient ischemic attack, positive family history etc[6]. But other less studied risk markers to predict asymptomatic atherosclerosis and incident ischemic stroke should also be identified.

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Peripheral arterial disease (PAD) affects some 12% to 14% of the general population, reaching 10% in people aged over 60 years and 20% aged over 75 years[7,8]. PAD caused by atherosclerosis is the most common cause of lower extremity ischemic syndromes in Western societies. Nearly half of those with PAD had concurrent coronary or cerebral vascular disease [9,10]. Even if patients with PAD are asymptomatic, they have an increased risk of future cardiac and cerebrovascular events, as well as being six times more likely to die within ten years when compared to healthy individuals. [11] .The association between peripheral arterial disease and increased mortality is a result of the fact that the underlying pathological process, atherosclerosis, is a systemic one. Atherosclerosis, if present in the periphery, is also likely in other parts of the arterial tree[12].The Fontaine classification provides a framework for clinical staging (from I to IV) of peripheral vascular disease[13]. Although intermittent claudication is the primary and most often the only symptom of peripheral vascular disease, unfortunately a vast majority of patients are asymptomatic and undiagnosed[14]. As a result, relying on clinical history has a very low sensitivity for determining the presence of peripheral arterial disease[15].

Therefore Ankle Brachial Pressure Index (ABPI), a simple noninvasive test done by Doppler assessment of the limb vessels to measure blood pressure in the legs relative to arms (as an approximation of central pressure), has been widely adopted for confirmation of a clinical diagnosis of peripheral arterial disease and its quantification[16].

Ankle Brachial Pressure Index (ABPI) is the ratio of tibial artery systolic blood pressure to brachial artery systolic blood pressure[17]. The normal range of ABPI is 0.91–1.3; ABPI > 1.3 or <0.9 is considered as high and low respectively; mild disease falls into the range of 0.7–0.9, moderate disease for ratios of 0.41–0.69 and ratios of less than or equal to 0.4 are quoted in severe disease[18].

A number of groups support the use of ABPI not only as a diagnostic tool, but also as a risk assessment tool in the setting of peripheral vascular disease[19-21]. In addition to diagnosing peripheral vascular disease, ABPI is also an indicator of generalized atherosclerosis because lower levels have been associated with higher rates of concomitant coronary and cerebrovascular disease, and with the presence of cardiovascular risk factors[22].

Moreover, the lower the ABPI value, the higher the risk of all-cause and cardiac and cerebrovascular death in patients with peripheral vascular disease[23]. Similarly an elevated ABPI more than 1.30 (even if the observation was non -diagnostic because of arterial incompressibility secondary to calcification) is also a predictor for an increase in all-cause as well as cardiovascular mortality[24].

However, some study reported a weak association between ABPI and ischemic stroke incidence after adjustment for other stroke risk factors[25].

The goal of this case-control study was designed, therefore, to determine the association of ankle brachial pressure index (ABPI) as a risk factor for ischemic stroke.

Materials and Methods:

This prospective observational case-control study of association between ankle brachial pressure index (ABPI) in patients with ischemic stroke was conducted who were admitted in the Department of Neurology and Medicine of Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh from July 2011 to June 2012 (1 year). Fifty(50) consecutive acute ischemic stroke patients and 50 age-sex matched patients other than stroke who have one or more vascular risk factors e.g. advanced age, male gender, positive family history, hypertension, diabetes mellitus, dyslipidemia, smoking, high BMI,previous history of stroke etc. were studied. Among them the stroke patients were considered as 'case' and patients without stroke were considered as 'control'. Inclusion criteria for cases were: (1) Patients with CT /MRI scan of brain proven acute ischemic stroke. (2)Patients having athero-thrombotic stroke. (3)Patients age more than 45 years (4) patients not having hemorrhagic stroke. cardioembolic stroke, deep vein thrombosis or acute limb ischemia and hypercoagulable state. The patient's age and sex match with the cases who fulfilled the criteria for at least 1 risk factors as advanced age, male gender, positive family history, hypertension, diabetes mellitus, dyslipidemia,

smoking, high BMI without stroke will be considered as control. Fifty clinically diagnosed patients of stroke, done by detailed history and examination, were further confirmed as having ischemic stroke by CT /MRI scan of brain. Then some relevant investigations and measurement of ABPI were performed. These patients were considered as case. The demographic, clinical and biochemical variables were compared with fifty age-sex matched control with appropriate statistical tools. Data were collected by a predesigned proforma. Patients information were obtained through using patients information sheets which involved questionnaire, clinical findings and biochemical findings, CT scan / MRI of brain and measurement of ABPI. All the cases and controls were informed about the nature of the study. Their informed written consent was taken in a consent form before collecting data. Proper permission was taken from the concerned departments and local ethical committee. The ABPI was measured in the Department of Cardiology of Sir Salimullah Medical College and Mitford hospital by a group of consultant cardiologists who are expert in performing Duplex vascular study by using a Doppler Echocardiography Machine (Vivid-7, general electric) with accompanying probe (8megaHz). All the cases and controls were informed about the nature of the study. Their informed written consent was taken in a consent form before collecting data. Statistical analyses related with this study were performed by use of SPSS 16.0 package program. The data was expressed by descriptive statistical methods like average, frequency distribution, percentage, mean & standard deviation as applicable. Comparison between groups was done by standard statistical test e.g. Chi-square test or other tests as applicable. Correlations between numeric variables, like Lipid profile, Blood glucose, Blood pressure, BMI were investigated by Pearson correlation test.

Results:

Regarding the age distribution of the study patients, the mean age was found 62.32±7.48 years in group I and 62.24±5.14 years in group II. Mean difference was not statistically significant (P>0.05) between two groups .

Regarding the sex distribution of the study patients, male was found 33(66.0%) in group I and 35(70.0%) in group II. Female was found 17(34.0%) and 15(30.0%) in group I and group II respectively. The difference was not statistically significant (P>0.05) between the two groups .

Table-I

Age distribution of the study patients (n=100)

Age (in years)	Group I(n=50)		Group II(n=50)		P value
	n	%	n	%	
d”50	2	4.0	2	4.0	
51-60	24	48.0	20	40.0	
61-70	18	36.0	26	52.0	
>70	6	12.0	2	4.0	
Mean ± SD	62.32±7.48		62.24±5.14		0.950^{ns}
Range (min-max)	(47-80)		(50-72)		

Group I: Case, Group II: Control . ns=not significant ,P value reached from unpaired t-test

Table II

Sex distribution of the study patients (n=100)

Sex	Group I(n=50)		Group II(n=50)		P value
	n	%	n	%	
Male	33	66.0	35	70.0	0.668^{ns}
Female	17	34.0	15	30.0	

ns= not significant .P value reached from chi-square test

Regarding the risk factors of the study patients, previous stroke was found in 4 cases (8.0%) in group I but not found in group II. H/O TIA was found in 2cases (4.0%) in group I but not found in group II. HTN was 38 cases (76.0%) in group I and 41(82.0%) in group II. DM was 26 cases (52.0%) and 29 cases (58.0%) in group I and group II respectively. IHD was 10(20.0%) cases in group I and 8(16.0%) cases in group II. Family history of stroke was 17(34.0%) cases in group I and 11(22.0%) cases in group II. Smoking/Tobacco was 37(74.0%) cases and 32(64.0%) cases in group I and group II respectively. The difference was not statistically significant (P>0.05) between two groups.

BMI <23 kg/m2 was found in 29(58.0%) patients in group I and 32(64.0%) in group II. BMI >23 kg/m^2 was found in 21(42.0%) patients in group I and 18(36.0%) patients in group II (Table IV). The difference was not statistically significant (P>0.05).

Table-III

Distribution of the study patients according to risk factors (n=100)

Risk factors	Group I(n=50)		Group II(n=50)		P value
	n	%	n	%	
Previous stroke					
Yes	4	8.0	0	0.0	0.058^{ns}
No	46	92.0	50	100.0	
H/O TIA					
Yes	2	4.0	0	0.0	0.247^{ns}
No	48	96.0	50	100.0	
HTN					
Yes	38	76.0	41	82.0	0.461^{ns}
No	12	24.0	9	18.0	
DM					
Yes	26	52.0	29	58.0	0.564^{ns}
No	24	48.0	21	42.0	
IHD					
Yes	10	20.0	8	16.0	0.602^{ns}
No	40	80.0	42	84.0	
Family history of stroke					
Yes	17	34.0	11	22.0	0.181^{ns}
No	33	66.0	39	78.0	
Smoking/Tobacco					
Yes	37	74.0	32	64.0	0.279^{ns}
No	13	26.0	18	36.0	

s= significant, ns= not significant. P value reached from chi-square test

Table IV

Distribution of the study patients according to BMI (n=100)

BMI (kg/m^2)	Group I(n=50)		Group II(n=50)		P value
	n	%	n	%	
d”23	29	58.0	32	64.0	0.538^{ns}
>23 21	42.0	18	36.0		

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

BP= Blood Pressure. Regarding the blood pressure of the study patients, mean systolic BP was found in 152.2±23.39 mmHg in group I and 134.4±26.2 mmHg in group II. Diastolic BP was found in 89.2±13.07 mmHg and 81.2±15.14 mmHg in group I and group II respectively. The mean difference was statistically significant (P<0.05) between two groups.

Regarding the mean RBS of the study patients, in group I, RBS was found 10.05±4.49 mmol/l and in group II, RBS was 9.77±3.91 mmol/l. The mean RBS difference was not statistically significant (P>0.05) between two groups .

Regarding the hypercholesterolemia of the study patients, hypercholesterolemia was found in 21(42.0%) cases in group I and 14(28.0%) cases in group II. The difference was not statistically significant (P>0.05) between two groups.

Regarding the ABPI of the study patients, normal (0.91-1.30) ABPI was found 37(74.0%) patients in group I and 45(90.0%) patients in group II. Low ABPI was found in 13(26.0%) patients in group I and 5(10.0%) patients (n=50)in group II. The difference was statistically significant (P<0.05) between two groups.

Mildly lower (0.70-0.90) ABPI was 9(18.0%) and 4(8.0%) in group I and group II respectively. Moderately lower (0.41-0.69) ABPI was found 4(8.0%) in group I and 1(2.0%) in group II.

Patients having IHD 3.00 (95% CI 3.05% to 44.32%) times more likely to have low ABPI (d"0.9).

Patients having carotid atherosclerosis 2.46 (95% CI 1.68% to 15.31%) times more likely to have low ABPI (<0.9).

Patients having ischemic stroke 3.91 (95% CI 1.87% to 33.18%) times more likely to have low ABPI (<0.9).

Patients having age >55 years, male gender, HTN, DM, Family history of stroke, smoking/tobacco chewing, BMI>23 kg/m^2 and hypercholesterolemia were not statistically significant (P>0.05).

Patients having carotid atherosclerosis 0.10 (95% CI 0.01% to 0.53%) times more likely to have ischemic stroke. Patients having low ABPI 7.91 (95% CI 1.58% to 39.49%) times more likely to have ischemic stroke. Patients having age >55 years, male gender, HTN, DM, IHD, Family history of stroke, smoking/ tobacco, BMI>23 kg/m^2 and hypercholesterolemia were not statistically significant (P>0.05) (Table X).

Table-V

Distribution of the study patients according to Blood Pressure (n=100)

Blood pressure (mmHg)	Group I(n=50) Mean± SD	Group II(n=50) Mean± SD	P value
Systolic	152.2±23.39	134.4±26.2	0.001^s
Range (min-max)	(110-200)	(100-190)	
Diastolic	89.2±13.07	81.2±15.14	0.001^s
Range (min-max)	(70-120)	(60-120)	

s= significant .P value reached from unpaired t-test

Table-VI

Distribution of the study patients according to Random blood sugar (n=100)

	Group I(n=50) Mean±SD	Group II(n=50) Mean±SD	*P* value
RBS (mmol/l)	10.05±4.49	9.77±3.91	0.740^{ns}
Range (min-max)	(5.2-21)	(5.4-19)	

RBS=Random blood sugar .ns= not significant .P value reached from unpaired t-test

Table-VII

Distribution of the study patients according to hypercholesterolemia (n=100)

Hypercholesterolemia	Group I(n=50)		Group II (n=50)		P value
	n	%	n	%	
Yes	21	42.0	14	28.0	0.142[ns]
No	29	58.0	36	72.0	

ns= no significant .P value reached from Chi-square test

Table-VIII

Distribution of the study patients according to ankle brachial pressure index (ABPI) (n=100)

ABPI	Group I(n=50)		Group II(n=50)		P value
	n	%	n	%	
Normal (0.91-1.30)	37	74.0	45	90.0	0.037[s]
Low	13	26.0	5	10.0	
Mild (0.70-0.90)	9	18.0	4	8.0	-
Moderate (0.41-0.69)	4	8.0	1	2.0	-
Severe (<0.40)	0	0.0	0	0.0	-

s= significant .P value reached from unpaired t-test

Table-IX

Multiple logistic regression models for risk factors associated with low ABPI (d"0.9).

	OR	95.0% CI for OR		P value
		Lower	Upper	
Age >55 years	0.25	0.00	9.34	0.453[ns]
Male gender	1.07	0.14	7.48	0.979[ns]
HTN	0.102	0.00	2.370	0.155[ns]
DM	1.18	0.14	9.51	0.872[ns]
IHD	3.00	3.05	44.32	0.005[s]
F/H of stroke	0.99	0.17	5.77	0.991[ns]
Smoking /tobacco	2.23	0.25	19.46	0.466[ns]
BMI (>23 kg/m^2)	0.52	0.09	2.84	0.453[ns]
Hypercholesterolemia	3.79	0.55	26.00	0.174[ns]
Carotid Atherosclerosis	2.46	1.68	15.31	0.026[s]
Ischemic stroke	3.91	1.87	33.18	0.002[s]

s=significant; ns=not significant

Table-X

Multiple logistic regression models for risk factors associated with Ischemic stroke.

	OR	95.0% CI for OR		P value
		Lower	Upper	
Age >55 years	0.75	0.16	3.41	0.716^{ns}
Male gender	0.43	0.11	1.68	0.225^{ns}
HTN	0.98	0.21	4.47	0.983^{ns}
DM	0.53	0.14	2.01	0.358^{ns}
IHD	0.28	0.04	1.73	0.173^{ns}
F/H of stroke	1.79	0.47	6.77	0.389^{ns}
Smoking/tobacco	2.34	0.56	9.69	0.239^{ns}
BMI (>23kg/m^2)	1.04	0.30	3.61	0.946^{ns}
Hypercholesterolemia	1.47	0.46	4.69	0.508^{ns}
Carotid Atherosclerosis	0.10	0.01	0.53	0.007^{s}
Low ABPI (<0.9)	7.91	1.58	39.49	0.012^{s}

s=significant; ns=not significant .

Discussion:

An ABPI ratio of less than 0.9 has been associated with up to a three-fold relative increase in cardiovascular mortality like ischemic stroke, IHD in both men and women[7,22,27]. Similarly, having an elevated ABPI >1.40 is a predictor for an increase in all-cause mortality as well as cardiovascular mortality like stroke and IHD[28].

However, relatively few data exist on the relationship between ABPI and stroke, and those studies have presented conflicting results, some showing that low ABPI independently predicted stroke risk, while other studies did not find such an association[20,32]. Furthermore, many of these studies were focused largely on a single race, gender, or a narrowly defined age group[29-31] . For these discrepancies the current study was conducted to evaluate the association of ABPI with ischemic stroke in the Bangladeshi population.

A total of 100 consecutive patients were enrolled in this study, out of which 50 patients with acute ischemic stroke and 50 patients having other than stroke were considered as group I (case) and group II (control) respectively. The present study findings were discussed and compared with previously published relevant studies.

In this current study in Table I was observed that the mean age was found 62.32±7.48 years with range from 47 to 80 years in group I and 62.24±5.14 years with range from 50 to 72 years in group II, which was almost similar between two groups. Most of the subjects were in 6th and 7th decade in both groups exploring that the association of low ABPI with ischemic stroke increase with age[33]. In a Thai study showed the mean age of all ischemic stroke patients was 63.5±14 years, 70.3±14.6 years in patients with abnormal ABPI and 61.9± 13.4 years in patients with normal ABPI[34]. Another study obtained the mean age was 64.04 ± 12.24 years in patients with normal ABPI and 70.48 ± 11.78 years in patients with abnormal ABPI[35]. A recent study showed that the median age was 64 years with range from 55 to 73 years in patients with normal ABPI and 71 years with range from 63 to 77 years in patients with abnormal ABPI[36]. The above findings are compatible with the current study.

In Table II regard showed that the sex incidence of the present study, it was observed that male was found 66.0% in group I and 70.0% in group II. A series of studies showed that male to female ratio was almost 2:1 in the whole study patients and male sex was associated with plaque score independently of other risk factors.[35-38] Similarly, male predominance also obtained[38].

Table III showed that the risk factors of the study patients, where previous stroke was found in

4(8.0%) patients in group I and H/O TIA was found in 2(4.0%) patients in group I but not found in group II. HTN was 38(76.0%) patients in group I and 41(82.0%) patients in group II. DM was 26(52.0%) patients and 29(58.0%) patients in group I and group II respectively. IHD was 10(20.0%) patients in group I and 8(16.0%) patients in group II. Family history of stroke was 17(34.0%) patients in group I and 11(22.0%) patients in group II. Smoking/Tobacco was 37(74.0%) patients and 32(64.0%) patients in group I and group II respectively. In a study documented that older age, previous history of stroke, TIA, diabetes mellitus, hypertension, ischemic heart disease, smoking and high BMI were considered as significant risk factors of stroke and abnormal ABPI[22]. In this series it was observed that previous stroke, H/O TIA, HTN, DM, IHD, positive family history of stroke and smoking / Tobacco chewing c were almost similar between two groups, no statistically significant (P>0.05) difference was found between the groups. Similar observations regarding the risk factors of stroke were also made[30,37,40].

For Asian people, BMI >23 kg/m^2 was considered as high BMI[41]. In Table IV this current study it was observed that BMI d"23 kg/m^2 was found in 58.0% patients in group I and 64.0% in group II. BMI >23 kg/m^2 was found in 42.0% in group I and 36.0% in group II. The difference was not statistically significant (P>0.05). A recent study mentioned that there were 7.4% patients who showed abnormal ABI (<0.90), and these patients were typically older and had a lower BMI[37]. In an another study it was observed that 75.0% and 72.7% patients were overweight in group I (stroke patients) and group II (control) respectively[40].

From Table V of this present study it was observed that the mean systolic blood pressure was found 152.2 ± 23.39 mmHg varied from 110 to 200 mmHg in group I and 134.4±26.2 mmHg varied from 100 to 190 mmHg in group II. The mean systolic blood pressure was significantly (p <0.001) higher in group I patients. On the other hand the mean diastolic blood pressure was found 89.2 ± 13.07 mmHg varied from 70 to 120 mmHg in group I and 81.2 ± 15.14 mmHg varied from 60 to 120 mmHg in group II. The mean diastolic blood pressure was significantly (p <0.001) higher in group I patients. But the presence of hypertension had no significant difference between two groups. This may be due to reactionary hypertension which occurs immediately after the stroke. These findings gave the emphasis over the blood pressure control as preventive measures of stroke and other cardiovascular events. The higher mean systolic and diastolic BP were also observed, where the mean systolic BP was found 173.0±16.0 mmHg and 162.0±8.0 mmHg in group I and group II respectively.[38] Similarly, the mean diastolic BP was found 98.0±8.0 mmHg in group I and 101.0±8 mmHg in group II, which are comparable with the current study.

In Table VI of this current series it was observed that the mean Random blood sugar (RBS) was found 10.05±4.49 mmol/l and 9.77±3.91 mmol/l in group I and group II respectively, which were almost similar between two groups. A recent study mentioned that there was a significant association of random blood sugar which was found 11.05±4.4 and 8.77±3.91 mmol/l in group I and group II respectively, which are comparable with the current study[41].

In Table VII this present series it was observed that hypercholesterolemia was found 42.0% in group I and 28.0% in group II, that was higher in group I but not statistically significant (P>0.05) between two groups. Similarly, a recrnt study showed hypercholesterolemia 40.3% in their study patients, which is similar with the current study.[43] In another studydocumented hypercholesterolemia 42.4% and 14.3% patients in group I (stroke patients) and group II (control) respectively, which is closely resembled with the current study[42].

In Table VIII Duplex study of the carotid arteries shows carotid arthrosclerosis was significantly higher in group I, where almost one third (32.0%) of the group I patients had atherosclerosis in the carotid arteries proved by the carotid artery duplex study and only 12.0% of group II patients had carotid atherosclerosis. Mild atherosclerosis was found 11(22.0%) patients in group I and 5(10.0%) patients in group II. Moderate atherosclerosis was 4(8.0%) patients in group I and 1(2.0%) patients

in group II. Severe atherosclerosis was 1(2.0%) patients in group I but not found in group II. The difference was statistically significant (P<0.05) between two groups. This indicates that the presence of carotid atherosclerosis was significantly associated with stroke. The finding of this present study was congruent with previous studies where severe extracranial disease was significantly associated with the incidence of ischemic stroke[36,43]. In Table IX, the Ankle Brachial Pressure Index (ABPI), it was observed that normal (0.91 – 1.30) ABPI was found nearly three fourth (74.0%) in group I patients and 90.0% in group II. Low ABPI was found more than one fourth (26.0%) in group I and 10.0% in group II. Low ABPI was significantly (p=0.037) higher in group I patients. It indicates that ischemic stroke was associated with low ABPI. Mildly lower (0.70-0.90) ABPI was 18.0% and 8.0% in group I and group II respectively. Moderately lower (0.41-0.69) ABPI was found 8.0% in group I and 2.0% in group II. Similarly, in a study reported that low ABPI was strongly associated with increased incidence of ischemic stroke[44]. In another study also showed significant association of ischemic stroke with low ABPI, which was similar with the current study; but the percentage of the low ABPI of the current study patients with stroke was higher (26.0%) with the above mentioned study (12.7%), which may be due to the ethnic variation[45]. In Singapore general hospital a study done and found that 26.0% patients with low ABPI have incident stroke, which is closely resembled with the current study. [36] In Asian people, possibly the prevalence of low ABPI is higher than the European people, although this should be determined in a large scale observational study in the Asian community. There might be another possibility that the current study and Singapore study were hospital based study and the American study was done in the community. This might be the cause of higher prevalence of low ABPI in these studies.

In Table X of this current study, it was observed in multiple logistic regression model that the patients who had ischemic stroke will have 3.91 times more likely to have low ABPI (d”0.9) with 95% CI 1.87% to 33.18%; (p<0.05). Patients who had IHD will have 3.0 times more likely to have low ABPI (d”0.9) with 95% CI 3.05% to 44.32%; (p<0.05). Patients who had carotid atherosclerosis will have 2.46 times more likely to have low ABPI (d”0.9) with 95% CI 1.68% to 15.31%; (p<0.05). On the other hand, patients with age >55 years, male gender, HTN, DM, family history of stroke, smoking/tobacco chewing, BMI >23 kg/m^2 and hypercholesterolemia were not statistically significant (P>0.05) with low ABPI in multivariate logistic model. In a recent study performed multivariate regression among ischemic patients and found that older age, hypertension, coronary disease, elevated systolic blood pressure, as well as low and borderline ABIs were all significantly associated with stroke[45].

In Table XI of this present study, it was observed in the multiple logistic regression model that the patients who had low ABPI will have 7.91 times more likely to have ischemic stroke with 95% CI 1.58% to 39.49%; (p<0.05). Patients who had carotid atherosclerosis will have 0.10 times more likely to have ischemic stroke with 95% CI 0.01% to 0.53%; (p<0.05).. Whereas patients with >55 years, male gender, HTN, DM, IHD, Family history of stroke, smoking / tobacco chewing, BMI (>23 kg/m^2) and hypercholesterolemia were not significantly (P>0.05) associated in multivariate logistic model. In a recent study found that after multivariate analysis, ischemic stroke was significantly correlated with abnormal ABI (OR 1.85; CI 1.05-3.28; P=0.033); male gender (OR 1.45; CI 1.08-1.95; P=0.014) and age e”60 years (OR 3.71; CI 2.63-5.24; P=0.001). The above findings are consistent with a current study[35].

In the Strong Heart Study the association between high ABI and mortality was similar to that of low ABI and mortality, highlighting a U-shaped association between this noninvasive measure of peripheral arterial disease and mortality risk. Death from all causes occurred in 23.3% of the study subjects and of these, 26.6% were attributable to cerebrovascular disease and Low ABI was present in 4.9%, and high ABI occurred in 9.2%[45.] . But the above mentioned findings were inconsistent with the findings of the current study.

Conclusion:

The present study data was showing a link between low ABPI with IHD, carotid atherosclerosis and ischemic stroke. So there is significant association of low Ankle Brachial Pressure Index (ABPI) in patients with Ischemic Stroke:

Disclosure: Conflict of interest: none

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REVIEW ARTICLE

A Review on Post Stroke Shoulder Pain Management

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Abstract:

Shoulder pain is critically important obstacle to functional recovery in most of the stroke sufferers. Hemiplegic shoulder pain causes considerable distress and reduced activity and can markedly hinder rehabilitation. The etiology of hemiplegic shoulder pain is probably multifactorial. The ideal management of hemiplegic stroke pain is prevention. For prophylaxis to be effective, it must begin immediately after the stroke. Awareness of potential injuries to the shoulder joint reduces the frequency of shoulder pain after stroke. The multidisciplinary team, patients, and care givers should be provided with instructions on how to avoid injuries to the affected limb. Shoulder strapping may be used to prevent shoulder pain. Over arm slings should be avoided. Treatment should include analgesics heat or cold therapy, electrical stimulation and pain free exercise as well. This review was done to find the recent developments in post-stroke shoulder pain management by extracting the published articles in this topic. The ultimate objectives were to delineate most rational and effective treatment options for post-stroke shoulder pain.

Introduction:

Shoulder pain has been reported to be one of the most common complications after stroke[1,2]. The incidence varies between 9% and 40% depending on patient group and study design[1-4]. Different studies have used various terms for shoulder pain, e.g., shoulder pain in hemiplegia[5–8],hemiplegic shoulder pain[9],and post stroke shoulder pain. Sometimes, it is unclear whether only proximal pain in the arm was assessed or if also more distal arm pain was included[10]. Shoulder pain hinders rehabilitation, is an important contributor to length of hospital stay[11],and has been associated with depression[4] and decreased quality of life[12].Several factors have been related to shoulder pain after stroke such as paralysis[3,4,13,14] ,restricted range of motion in the shoulder[5,6,13],spasticity[7,8],right hemispheric cerebrovascular lesion and left hemiplegia[6,8],sensory abnormalities[4,8],diabetes mellitus[3],low Barthel Index score[11],and inappropriate handling of the patient[9]. Recovery from shoulder pain may occur in 80%[4]. A common sequel of stroke is hemiplegic shoulder pain that can hamper functional recovery and subsequently lead to disability. Poduri reports that hemiplegic shoulder pain can begin as early as 2 weeks post stroke but typically occurs within 2-3 months post-stroke[15].The cause of hemiplegic shoulder pain is the subject of considerable controversy. The following processes have all been postulated as causes of a painful hemiplegic shoulder: glenohumeral subluxation, spasticity of shoulder muscles, impingement, soft tissue trauma, rotator cuff tears, glenohumeral capsulitis, bicipital tendinitis, and shoulder hand syndrome. The etiology of hemiplegic shoulder pain is probably multifactorial. Chae and coauthors indicated that the amount of motor recovery is related to the degree of initial severity and the amount of time before voluntary movements are initiated[16, 17].

Factors contributing to pain

Subluxation and spasticity: Wanklyn and coauthors found no association between the severity of subluxation and the degree of pain[18].Numerous cases of subluxation without pain have been documented, as have cases of a painful shoulder without subluxation. Spasticity is defined as a velocity-sensitive disorder of motor function causing increased resistance to the passive stretching of muscles and hyperactive muscle stretch reflexes. Van Ouwenaller and colleagues identified spasticity as a prime factor and one of the most common causes of shoulder pain in patients with

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hemiplegia[19]. Compared with patients who have flaccidity, patients with spasticity seem to experience a much higher incidence of shoulder pain, which is thought to result from muscle imbalance.

Complex regional pain syndrome

The incidence of Complex regional pain syndrome (CRPS) varies in the literature. Davis and coauthors reported that CRPS occurs in 12.5% of patients who have had a stroke, while Chalsen and colleagues reported the incidence to be 61%[20].Onset of CRPS is within 3 months post stroke and rarely after 5 months post stroke. In a study, Davis and coworkers demonstrated that of those patients who developed CRPS, 65% had done so by 3 months post stroke, and 98% had done so by 5 months post stroke[21].

Adhesive capsulitis

Glenohumeral capsulitis is postulated to play an important role in hemiplegic shoulder pain. Patients usually present with pain and limited passive movement of the shoulder, especially external rotation and abduction. Joynt reported that adhesive changes may reflect a later stage in the recovery process, when chronic irritation or injury, inflammation, or lack of movement eventually results in adhesions[22].

Patients with hemiplegia who have their flaccid arm in an unsupported, dependent position or patients who have been inappropriately transferred by pulling on the arm, tend to be at increased risk for traction neuropathy. Kaplan suggested that plexus injury should be considered in a patient who has atypical return of distal function[23].

Neglect

Joynt reported that neglect may lead to increased trauma or disturbed perception of the quality of the pain, thereby producing a sensation of pain without the usual pathology[22].Snels and coauthors found that on numerous occasions, patients with sensory deficits, visual field deficits, or neglect more commonly experienced recurrent injuries of the shoulder, possibly contributing to capsulitis[24].

Diagnosis: Diagnosis can be confirmed through history of stroke and excluding pre stroke pathology.

A Common findings of the shoulder and upper extremity (UE) reported by patients with hemiplegia include painful restricted range of motion, mild swelling and tenderness.

Management update: Most effective and rational treatment options should address the factors contributing to pain first, the pain and function.

Glenohumeral subluxation

Treatment of subluxation by reduction remains a controversial means of controlling shoulder pain. Slings, arm boards, troughs, and lap trays have not proven to be effective and, in some cases, may result in overcorrection. Sling use also may cause lateral subluxation, impair proprioception, interfere with functional activities, or promote undesirable synergy patterns; furthermore, sling use may not prove beneficial in preventing shoulder subluxation. Neuromuscular electrical stimulation (NMES), has proven moderately successful in the prevention and treatment of subluxation[25,26]. Yu and colleagues demonstrated that NMES causes substantial reduction in subluxation and, possibly, enhancement of motor recovery and reduction of shoulder pain[18, 27].

Spasticity management: The mainstay of treatment for spasticity begins with physical therapy and the use of ROM and stretching exercises, Overaggressive stretching or ROM should be avoided during the rehabilitation process[28]. Proper positioning also is used as a means of controlling spasticity, by suppressing the evolution of synergy patterns. Botulinum toxin also is preferred when the desired outcome is for slower onset with shorter duration[29,30].This procedure is sometimes used when the subscapularis and pectoralis major muscles require nerve block. Chironna and Hecht felt that motor block to nerves innervating internal rotators would help relieve the pain caused by internal rotation synergy[31].

Complex regional pain syndrome

Treatment options are numerous and physical therapy is the cornerstone. ROM exercises, optimal positioning of the limb, and the avoidance of painful stimuli are all suggested. Other treatments might include non-steroidal anti-inflammatory drugs (NSAIDs), modalities such as electrical nerve

stimulation or ultrasonography), a short course of oral steroids, or a ganglion block.

Adhesive capsulitis

Treatment of adhesive capsulitis usually involves therapeutic exercise, manual mobilization exercises, analgesics, and possibly steroid injections. Treatment for traction injuries is limited to the use of supportive care until the return of function.

Subacromial bursitis.

Early treatment with physical modalities, NSAIDs, steroid injections, and ROM exercises is advocated for the reduction of symptoms and prevention of later complications.

Neglect-related pain

Treatment options suggested by Lorish and colleagues include caloric stimulation, prism glasses, visuospatial cueing, computer-assisted training, and compensatory strategies[32].

Physiotherapy: Physiotherapy has been used in the treatment of hemiplegic shoulder pain[33]. There are two major approaches to therapy in this field: those that focus on the problem as a localized mechanical one; and those that view the problem as a neurological one. Local treatments used have included heat and cold therapy[34, 35, 36]. Slings and shoulder supports have also been used[37, 38]. Other physiotherapy approaches include those of Bobath, Brunnstrom, and proprioceptive neuromuscular facilitation. Until recently, the evidence for the effectiveness of these methods of physiotherapy has been poor[34].

In patients with hemiplegia, ROM of the shoulder is usually lost early, so Hanger and colleagues recommended that preventive treatments begin as soon as possible, usually within the first 1-2 days post stroke[39].Arm support and preservation of joint ROM is performed through early passive motion.

Biofeedback: Biofeedback is based on muscular relaxation and/or reeducation by verbal, visual, sensory, or auditory responses. Biofeedback is used in an attempt to relax the antagonist muscles, subsequently allowing the opposed agonists to function more effectively. In order to reeducate the upper extremity, the spastic scapular and glenohumeral antagonist muscles need to be released in order for the agonists to work more proficiently.

A common type of biofeedback, which was first introduced in 1960, involves the use of EMG for neuromuscular reeducation. Overall, trials involving EMG biofeedback have shown mixed results, and its cost-effectiveness is uncertain. However, a meta-analysis by Schleenbaker and Mainous showed it to be an effective tool for neuromuscular reeducation and improving functional outcomes in stroke patients with hemiplegia[40].

Proprioceptive neuromuscular facilitation

Developed by Kabat, Knott, and Voss, proprioceptive neuromuscular facilitation (PNF) involves repeated muscle activation of the limbs by quick stretching, traction, approximation, and maximal manual resistance in functional directions (ie, spiral and diagonal patterns) to assist with motor relearning and increasing sensory input. Lorish and coauthors have considered it to be an optimal method of stretching in patients with hemiplegia[32].Numerous clinical trials have not proven that application of any one facilitative approaches improves patient outcome over conventional therapy[41-46].

Constraint-induced movement therapy

Constraint-induced movement therapy (CIT) is a family of therapies that induce patients who have had a stroke to greatly increase the amount and quality of movement of their paretic limb, in turn improving function. CIT is based on the theory of “learned nonuse,” first described by Wolf and colleagues[47] and later by Taub and coauthors[48].Researchers subsequently concluded that the use of CIT proved to be an effective means of restoring substantial motor function in chronic stroke patients.

Prevention

Without appropriate care, patients with hemiplegia have an increased risk of developing numerous shoulder complications, including nerve pressure palsies, nerve traction injuries, rotator cuff pathology, capsulitis, impingement syndromes, or subluxation. Strapping also has been studied as a

means for shoulder support. Theoretically, it should support the glenohumeral joint or reduce subluxation while allowing the upper extremity to move freely.

A study by Hanger and colleagues concluded that strapping the shoulder did not significantly preserve ROM or reduce the prevalence of subluxation over a 6-week trial, even when done concomitantly with standard physical therapy[39].

Prognosis

Carr and Kenney reported that about two thirds of all stroke survivors will be disabled, up to 50% will be severely disabled, and 10-15% will require institutional care[49].Motor weakness also is reported in 50-80% of post stroke survivors. Brandstater reported that most spontaneous recovery of voluntary motor function occurs in the first 2-3 months following stroke. However, it can occur years later[50].

Cailliet reported an unfavorable prognosis for complete upper extremity motor recovery if the flaccid stage lasts longer than 2 weeks,[51] Other unfavorable predictors in estimating functional recovery include excessive spasticity and impaired sensation and perception,[52]Depression also can contribute to unfavorable outcome, with Wanklyn and coauthors reporting a 22-27% incidence within the first few weeks post stroke[53].

Conclusion: Hemiplegic shoulder pain affects stroke outcome in a negative way. It interferes with recovery after a stroke: it can cause considerable distress and reduced activity and can markedly hinder rehabilitation. Hemiplegic shoulder pain has been associated with prolonged hospital stay and poor recovery of arm function in the first 12 weeks after stroke. Depression and reduced quality of life among patients after stroke with pain has been described, but it has not been clearly established if these factors are directly related to the severity of pain, higher degree of impairment, or other factors. Important outcomes include pain relief, improved passive and active range of motion and arm function Indications for surgery in patients with hemiplegic shoulder pain include failure of conservative treatment and pain of such intensity that it interferes with skin hygiene or prevents participation in rehabilitation.

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