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CONTENTS

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- Review articles are subject to the peer review process. They should contain a maximum of 4000 words and 75 references.
- Original papers should have a structured abstract, must not exceed 3,000 words and should not include more than 4-6 illustrations and tables. Each separate part of a figure (a, b, etc.) counts as an illustration. Up to 40 references are permitted.
- Brief communications should include brief original studies or reports on one or a small number of cases. They should not exceed 1,000 words; 1-2 illustrations and up to 10 references are permitted.
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Bangladesh Journal of Neuroscience 2019; Vol. 35 (1): 1-9

ORIGINAL ARTICLES

Migraine Headache: A Bangladesh Perspective

AHMED KGU[1], MAHMUD R[2], ISLAM MR[3] ,CHOWDHRUY AH[4], ALAM I[5], RASSEL M[6], MONAYEM FB[7]

Abstract:

Background: *Migraine headache is one of the commonest cause of primary headache. This study aims to reveal the clinical profile of migraine headache in Bangladeshi people presented in Headache clinic, Dhaka Medical College Hospital. It will give an overview on presentation of migraine and its functional consequences among the people of Bangladesh.* ***Methods:*** *The study was a hospital based cross sectional observational study. It was conducted in the Headache clinic Dhaka Medical college Hospital from January 2018 to December 2018. About 854 patients with headache was attended in the headache clinic during the study period. Of that 234 patients were diagnosed as migraine according to ICHD-3 classification and 75 patents were enrolled in this study by systematic sampling. Details were collected using a preformed questioner.* ***Results:*** *In this study migraine burden among the headache patients found to be about 25%.The mean age of the onset of the migraine headache in this study was found to be 25.2±11.86 years, in most of the cases (4 68%) in 15-34 years age group. In this study 36% of the patient with migraine had positive family history which is significantly higher in patients with migraine with aura (52% vs. 30% p value <0.5). In this study about 81% of the patient has single or multiple trigger factors. Along with other known factor sun exposure and journey was found to be the important trigger factors for Bangladeshi population. In this study 22% of the female migraineurs and 33% of male migraineurs had aura. About 53% of the patient with aura had combinations of aura and 47% patient had exclusive visual aura. In the present study 100% of the patient had visual aura, 42% had brainstem aura and 10% had sensory aura. The study revealed that 25% patient had chronic daily headache due to migraine, 26% patient had >5 attack/ month and 15% patient had < 4 attack per month. In this study 44% had moderate headache and 56% had severe headache according to VAS score. Chronic migraine with anxiety, chronic migraine with medication overuse Migralepsy, Status migrainosus were found as a complications of migraine in this study. According to MIDAS score Patient largely had Mild (32%) to Moderate (34.67%) disability.* ***Conclusions:*** *Clinical profile of migraine in Bangladesh differs in some trigger points and migraine subtypes than the western world. Sun exposure and journey found to be most important triggers. Migraine with brainstem aura occurs in a significant number of the patient.*

Keywords: *Headache, Migraine with aura, Migraine without aura etc.*

Introduction:

Primary headache disorders are among the commonest disorders, affecting people in all countries. Estimate is that one person in three experiences severe headache at one stage of their life. Life time prevalence of any type headache as estimated from population based studies is more than 90% for man and 95% for the women[1].

Migraine is one of the important causes of primary headaches. Migraine has a one-year period

1. Dr. Kazi Gias Uddin Ahmed, Associate Professor and Head, Dept. of Neurology, Dhaka Medical College. Dhaka, Bangladesh.
2. Dr. Reaz Mahmud, Assistant Professor, Dept. of Neurology, Dhaka Medical College. Dhaka, Bangladesh.
3. Prof. Dr. Md. Rafiqul Islam, Professor & Chairman, Dept. of Neurology, Bangabandhu Sheikh Mujib Medical University.
4. Dr. Ahmed Hossain Chowdhury, Associate Professor, Dept. of Neurology, Dhaka Medical College. Dhaka, Bangladesh.
5. Dr. Iftekher Alam, Assistant Professor, Dept. of Neurology, Dhaka Medical College. Dhaka, Bangladesh.
6. Dr. Mohammad Aftab Rassel, MD Thesis Student, Dept. of Neurology, Dhaka Medical College. Dhaka, Bangladesh.
7. Dr. Farhana Binte Monayem, Medical officer, Sarkari Karmachari Hospital, Dhaka, Bangladesh.

prevalence of 12 percent (17.1 percent in women and 5.6 percent in men)[2]. The cumulative incidence of migraine by age 85 is 18.5 percent in males and 44 percent in females[3].

Migraine is a neurovascular disease characterized by a broad spectrum of symptoms, varying from headaches that are typically unilateral and have a pulsating quality, associated with various neurological symptoms such as nausea, increased sensitivity to light and sound (photophobia and phonophobia), and aura, which may consist of visual, sensory or motor disturbances[4]. (The International Classification of Headache Disorders, 3rd edition beta version, 2013).

Migraine Headache is broadly classified into migraine with aura and migraine without aura. They are diagnosed according to The International Classification of Headache Disorders, 3rd edition beta version, 2013[4]. Migraine with aura and migraine without aura are genetically distinct. Migraine with aura (MA) is a prevalent neurological condition with strong evidence for a genetic basis[5].The susceptibility gene loci for migraine with aura and without aura are different[6, 7].

The clinical picture of migraine is composed of 4 different stages including the prodromal stage, aura stage, headache stage and postdrome stage. Migraine headache also has some established trigger factor[8]. Clinical profile of migraine varies person to person, country to country even in the same person. Most of the study regarding clinical profile was done in the developed countries. There is scarcity of the study revealing clinical profile in Bangladesh.

This study aims to reveal the clinical profile, trigger factor, Complication functional disability, severity of migraine headache in Bangladeshi people presented in Headache clinic, Dhaka Medical College Hospital. It will give an overview of presentation of migraine and its functional consequences on the people of Bangladesh.

However through this study it would be known whether the findings of other study done in abroad could be replicated or not. So it would give some light whether presentation of *migraineurs* in our country is same or different from other population. Thus the findings of this study will invoke further research as well about migraine.

Methods:

The study was a hospital based cross sectional observational study. It was conducted in the Headache clinic Dhaka Medical college Hospital from January 2018 to December 2018. Institutional ethical committee approval was obtained.

Patient presented in the headache clinic, Neurology department, Dhaka Medical College Hospital was labeled as migraine by experienced Neurologist. Migraine with or without aura was defined according to International classification of headache disorders[4].Patientof both sexes and all ages fulfilling the ICHD 3 criteria were included in the study. Migraine patient with other cause of headache like sinusitis, post traumatic headache and drug induced headache, were excluded from the study. Patients were enrolled by Systematic Sampling Method. Every 3rd patient with migraine headache attended in a headache clinic day was enrolled in this study. Every patient was coded by the researcher. An informed written consent was obtained from the patients. Face to face interview was conducted by using a semi structured questionnaire containing socio-demographic parameters and relevant information about Migraine. Detailed fundus examination was done in all patients. Severity of migraine was assessed using Visual Analogue scale 1-10. Migraine Disability Assessment was done using MIDAS score. Secondary causes of headache were excluded using brain imaging in suspected patients The Data was collected by Research Assistant, who will be a trained Doctor. Variables of the collected data were uploaded in Microsoft excel sheet. The data was analyzed by using simple descriptive statistics like mean, median and prevalence rates, standard deviation. Chi square rest was done to observe the significance.

Results:

About 854 patients with headache were attended in the headache clinic during the study period. Of that 234 patients were diagnosed as migraine and 75 patents were enrolled in this study by systematic sampling.

Table-I

Variables recorded in the clinic questionnaire

Name of the Variables	
Age at the presentation	Duration of aura
Age at the onset of the symptoms	Aura subtype
Sex	Postdrome symptoms
Family history	Headache character
	Site
	Duration
	Frequency
Trigger factors	Phobia
Prodrome symptoms	Co- Morbidity
Pain Severity VAS (1-10)	Migraine Disability Assessment score (MIDAS)

Table-II

General characteristics of the study population

Traits	Results
Mean Age of the Study population	31.4±12.5 Years
Mean age of onset of Headache	25.2±11.86 years
Sex Distribution	
Male	21(28%)
Female	54(72%)
Family History	27(36%)
Positive with Aura patient	10(52%)
Positive without Aura patient	17(30%)
	P value <0.5
Migraine subtypes	
Migraine without Aura	53(70.67%)
Migraine with Aura	18(24%)
Migraine aura sine Headache	1(1.33%)
Special form of childhood Migraine	3(4%)
Benign cyclical vertigo	1(1.33%)
Abdominal Migraine	1(1.33%)
Cyclical vomiting syndrome	1(1.33%)
Headache duration	17.6±16.12hours
Duration of aura	31.34 minutes
Number of Aura (among the aura patient)	
Single Aura	10(47%)
Multiple Aura	9(53%)
Duration of prodrome	2.26 hour
Phobia	71(96.67%)
Nocturnal Arousal due to headache	28(37.33%)
VAS Severity score	7.24±1.67
MIDAS severity score	7.78±5.9
Complications of migraine	28(37.33%)
Co-morbidity	32(42.66%)

Mean age of the study population at presentation was 31.4±12.5 Years. Onset of Headache occurred at 25.2±11.86 years. Most of the study population (72%) were female. About 36% of the study population had positive family history which is significantly common in migraine with aura patient.. Most common migraine subtype was Migraine without aura (70.67%). Duration of headache was on average 17.6 hour, duration of prodrome was 2.26 hours and duration of aura was 31.34 minutes. In 47% cases patient presented with single aura and in 53% cases patient presented with multiple aura. Phobia associated in most of the cases. Quiet a large number of the patient (37.33%) had history of nocturnal arousal due to headache. About 37% of the patient had migraine complication and 42% patient presented with different co-morbidity.

Most of the patient is in the age group of 19-38.Most of the study population in this age group is female.

Onset of migraine occur in 15-24 and 25-34 age group with significantly higher in female patient

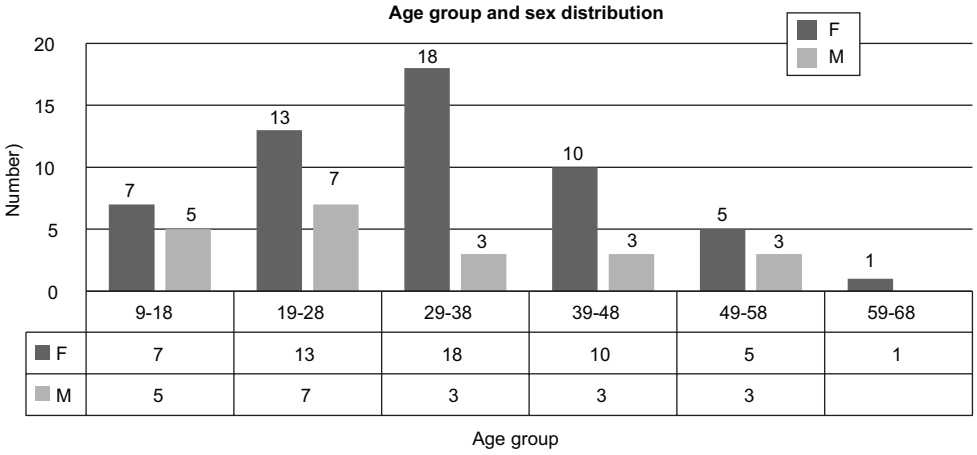


Fig.-1: *Age group and sex distribution of the patient at presentation*

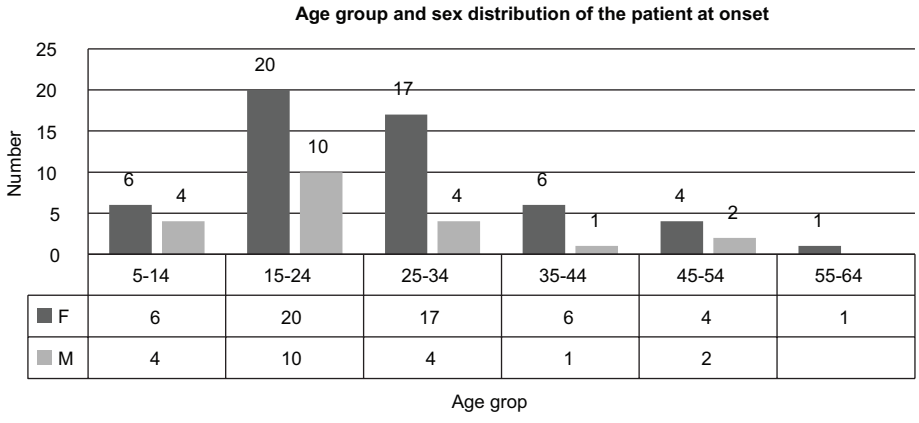


Fig.-2: *Age group and sex distribution of the patient of at onset*

Table-III

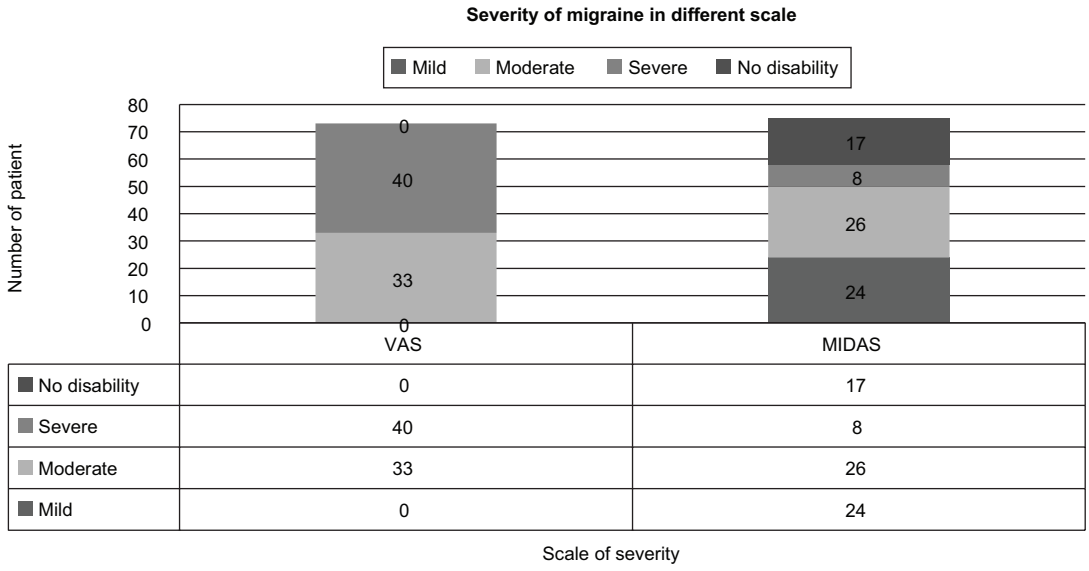
Characteristics of headache

Trait	Number (Percentage with grand total)		
	Male	Female	Total
Site of headache			
Unilateral	10(13.33%)	16(21.33)	26(34.67%)
Bilateral	6(8%)	32(42.67%)	38(50.67%)
Alternating	1(1.33)	6(8%)	7(9.33%)
Frequency of headache(most common)			
2/week	6(8%)	14(18.67%)	20(26.67%)
7/week	3(4%)	16(21.33%)	19(25.33%)
3/week	4(5.33%)	7(9.33%)	11(14.67%)
1/week	5(8%)	6(6.67%)	11(14.67%)
Aura subtype(among the patient with Aura)			
Visual	7(36%)	12(64%)	19(100%)
Brain stem	6(66%)	2(10%)	8(42%)
Motor	1(5%)	0	1(5%)
Sensory	0	2(10%)	2(10%)
Phobia subtype			
Photophobia	17(22.6%)	52(69.1%)	69(91.77%)
Phonophobia	13(17.29%)	36(47.88%)	49(65.17%)
Osmophobia	2(2.67%)	12(15.96%)	14(18.62%)
Complication			
Absent	17(22.67%)	30(40%)	47(62.67%)
Present	4(5.33%)	24(32%)	28(37.33%)
• Chronic migraine with anxiety	2(2.67%)	14(18.67%)	16(21.33%)
• Chronic migraine with Medication overuse	1(1.33%)	7(9.33)	8(10.67%)
• Migralepsy	1(1.33%)	1(1.33%)	2(2.67%)
• Status Migrainosus	0	2(2.67%)	2(2.67%)

Most of the patient presented with either unilateral (34.67%) or bilateral headache (50.67%). In episodic migraine most of the patient's frequency of headache was 2/week (26.67%). On the other hand 25.33% of the patient had headache in almost all the days in a week that is chronic daily headache. Visual aura (100%) was the most prevalent aura subtype followed by Brainstem aura (42%).Almost all the patient had photophobia (91.77%). About 37% of the patient presented with migraine complication and chronic migraine with anxiety (21%) was the most prevalent complication. Complications were more prevalent among the female.

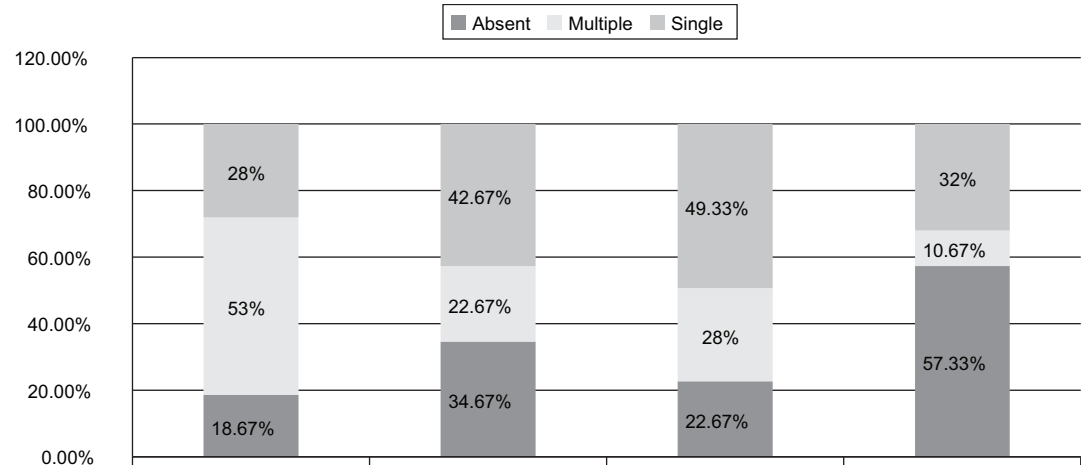
Pain is largely Moderate (44%) to severe (56%)in VAS scale. According to MIDAS score patient largely had Mild (32%) to Moderate (34.67%) disability.

In most of the cases patient had multiple trigger factors (53%). In most of the cases prodrome (42.67%), postdrome (49.33%) and co-morbidities (32%) were single.



	VAS	MIDAS
No disability	0	17
Severe	40	8
Moderate	33	26
Mild	0	24

Fig.-3: *severity of migraine in different scale*



	Trigger factor	Prodrome	Postdrome	C0-morbidity
Single	28%	42.67%	49.33%	32%
Multiple	53%	22.67%	28%	10.67%
Absent	18.67%	34.67%	22.67%	57.33%

Fig.-4: *Frequency of the trigger factors, prodrome, postdrome and co-morbidity*

Trigger factors were present in 81.33 %(61) of the patient. Of that Sunexposure (37.70%), anxiety (32.79%), insomnia (37.70%) and journey (31.11%) were common. Prodrome were present in 65.33% ofthe cases. Neckstiffness (67.34%) and Irritability (42.85%) were the most prevalent symptoms. Postdrome were present in 77.33 % cases. Among them Lack of concentration and Mood change were the prevalent symptoms. About 42% of the patient presented with co-morbidity. Generalized anxiety disorder (37.5%), NUD (21.8%) and Hypertension (25%) were the most common co-morbidity.

Table-IV

Common trigger factors, prodrome and postdrome symptoms

Trigger factors		Prodrome		Postdrome		Co-morbidity	
Sun exposure	23 (37.70%)	Neck stiffness	33(67.34%)	Lack of concentration	24 (41.37%)	Hypertension	8(25%)
Anxiety	20(32.79%)	Fatigue	11(22.44%)	Mood change	21(36.20%)	Diabetes	4(12.5%)
Insomnia	23(37.70%)	Irritability	21(42.85%)	fatigue	18(31.03%)	Depression	4(12.5%)
Journey	19(31.11%)	Craving for food	2(4%)	sleep	22(37.93%)	Generalized anxiety disorder	12(37.5%)
Temperature change	10(16.39%)	Sleepiness	4(8.1%)			Non-Ulcer dyspepsia	7(21.8%)
Sound	11(18.03%)	Yawing	2(4%)			Psycogenic Dyspnoea	2(6.2%)
Stress and exertion	8(13.11%)					Psycogenic vertigo	4(12.5%)
Menstruation	7(11.47%)						

Discussion:

Migraine is one of the important primary headache disorders. Globally migraine burden among the headache patients is about 11-15%[9, 10]. In this study migraine burden among the headache patients presented in headache clinic found to be about 25%. This is a little bit higher as it was a hospital based study, mild Tension type headache in most of the cases don't appear in Hospital.

The mean age of the onset of the migraine headache in this study was found to be 25.2±11.86 years, in most of the cases (4 68%) they presented in 15-34 years age group. It is found that mostly migraine starts before the age of 40[1, 11]. Like other study[11, 12, 13] females are the worst suffer of the migraine in the present study as well (F: M 2.6:1).

Migraine is largely a familial disorder. In this study 36% of the patient with migraine had positive family history which is significantly higher in patients with migraine with aura (52% vs. 30% p value <0.5).

Migraine has several known trigger factors. In this study about 81% of the patient has single or multiple trigger factors. Along with other known factor sun exposure and journey was found to be the important trigger factors for Bangladeshi population. Bangladeshi female usually do not take alcohol and pure chocolate intake is less among Bangladeshi population. So these factors as a trigger were not found in this study. This study revealed that about 11% of the patient had catamenial migraine which include both cyclical and non-cyclical form. According to MacGregor[15], the prevalence of cyclical catamenial migraine is 7.2%.

Migraine headache started with prodrome which persist for hours to days[1]. In this study 65% of the patient had prodrome which persisted for average 2.21 hour. A significant number of the patient had multiple prodrome (422%). Neck stiffness and irritability was the most prevalent prodrome.

Migraine headache is broadly classified as migraine with aura and without aura. Inthis study 24% of the patient with migraine had aura. In USA 30.8 percent of female migraineurs and 32 percent of male migraineurs have aura[16]. In this study 22% of the female migraineurs and 33% of male migraineurs had aura. .Four special form of migraine (Cyclical vomiting syndrome, Abdominal migraine, Benign cyclical vertigo, Episodic torticollis) are found in Pediatric population[1]. In this study abdominal migraine benign cyclical vertigo and cyclical vomiting syndrome was found.

Among the Patient with aura 99 percent has a visual aura. Most (60%) patients has a combination of aura symptoms, 39 percent has a visual aura exclusively. When more than one aura symptom occurred, they occur in succession in 96 percent

and simultaneously in four percent of patients[17]. In this study 53% of the aura patient had combination of aura and 47% patient had exclusive visual aura. In the present study 100% of the patient had visual aura, 42% had brainstem aura and 10% had sensory aura. Aura symptoms usually persist for 5-60 minutes. In this study Average duration of aura was 31 minutes.

Migraine pain is unilateral in 60 percent of cases and bilateral in 40 percent. About 15 percent of the patient migraine always occurring on the same side[18]. In this study about 50% patient had bilateral headache, 35% patient had unilateral headache and 10% cases had alternating headache (ie. Stared unilaterally and then become bilateral). Migraine headache usually persisted for 4-72 hours. In this study average duration of headache was about 18 hours. Migraine headache is by definition moderate to severe headache. In this study 44% had moderate headache and 56% had severe headache according to VAS score.

Frequency of migraine attack varies in different study. In a study among the neurologist it was found that ,25 percent, four or more severe attacks a month; 35 percent, one to four severe attacks per month; 38 percent, one or less severe attacks per month; and 37 percent, five or more headache days per month.[19]. In this study 25% patient had chronic daily headache, 26% patient had >5 attack/ month and 15% patient had < 4 attack per month.

In almost all cases migraine is associated with phobia. In this study 92% patient had photophobia and 62% had phonophobia.

Postdrome is the fourth and final phase of a migraine attack. For those having a severe migraine episode, the shift from headache to postdrome can be difficult to identify. Postdrome usually persist < 24hour. In one study it is found that 90% patient had postdrome, 67% patient had loss of concentration and 75% has tiredness[20]. In this study 77% patient had postdrome symptoms, of which lack of concentration is found in 41%, fatigue in 36% and mood change in 36% of cases.

Co-morbidity makes migraine management challenging. In this study bout 42% of the patient presented with co-morbidity. Functional co-morbidity (Generalized anxiety disorder, Depression, NUD, Rage attack) is the most prevalent in this study.

Migraine poses a significant impact in the daily life of the migraineurs due to its complications and functional disability.

Chronic migraine with anxiety, chronic migraine with medication overuse, Migralepsy, Status migrainosus were found as a complication of migraine in this study. In this study a significant number of the patient was found with medication overuse (10%).

Functional disability in this study was assessed with MIDAS score. As patient had to recall the previous 3months events the findings might not be representative. According to MIDAS score Patient largely had Mild (32%) to Moderate (34.67%) disability, 8% patient severe disability.

This study characterizes patients with headache disorders who sought medical treatment with a headache neurology specialist. Therefore, it is inappropriate to generalize the results of this study to headache disorders in the community.

In some cases patient had to recall previous events. There was possibility of recall bias in this study.

Conclusion:

Migraine is a disease that occurs in the age when someone remain most active. Migraine causes a significant morbidity. Proper diagnosis, assessment of the severity, detection of the trigger factors, counseling would be the cornerstone of migraine management. To make a plan and guideline of management, clinical profile of the disease of the respective population is the paramount importance. This study was the attempt to know the profile of migraine in Bangladeshi population. In this study it was found that some trigger factors are new for us. Migraine with brainstem aura occurs in a significant number of the patient where as it is rare in the western countries. It will evoke further research among the patient with migraine.

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Bangladesh Journal of Neuroscience 2019; Vol. 35 (1): 10-13

Demographic Pattern of Alzheimer's Disease in Bangladesh

ROY NR[1], KHAN MRK[2], MIAH MBA[3], ISLAM MR[4], MAJUMDER B[5], DAS S[6], UDDIN MK[7], HAQUE MA[8], SARKER I[9]

Abstract:

Background: *AD is the most common cause of dementia in elderly which causes economic burden for the affected individual, caregivers and society. The objective of this study was to see demographic characteristics among AD patients and it will provide magnitude of the problem and planning of health programme for prevention of disease.* ***Methods:*** *This observational analytical study was carried out in the Neurology ward, OPD and Dementia clinic of BSMMU, Dhaka from May' 15 to February' 17. A total of 45 patients were recruited as study population after satisfying all the criteria for enrollment.* ***Results:*** *A total of 27 male and 18 female with mean age of 69.20 ± 11.16 years, constituted as cases.* ***Conclusion:*** *The occurrence of AD found more after the age of 65 years. The present study found that lower educational level is associated with more chance of getting AD. Higher rate of Alzheimer's disease was found in older man than women.*

Keywords: *Dementia, Alzheimer's Disease, Demographic characteristics etc.*

Introduction:

Alzheimer's disease (AD) is a specific neurodegenerative disease and is the most common cause of dementia in old people. Clinically, it is characterized by loss of memory, inability to learn new things, loss of language function, a deranged perception of space, inability to do calculations, indifference, depression, delusions, and other manifestations. These deficits affect patients' social functioning and make it difficult or impossible for them to carry on with daily living. AD is relentlessly progressive and fatal within 5 to 10 years. AD patients usually die of complications of chronic illness. AD is the fourth to fifth most common cause of death in the United States. Sometimes AD involves people in their 40s and 50s, but is mainly a disease of old age. It's incidence is 1.2 per 1000 person years among 65–69-years, increasing to 53.5 in those >90 years and prevalence is 4.4% in those >65 years. Affects females more than males; most common >65 years[1].

With the exception of cases of Alzheimer's caused by genetic abnormalities, experts believe that Alzheimer's, like other common chronic diseases, develops as a result of multiple factors rather than a single cause. The greatest risk factors for late-onset "sporadic" Alzheimer's are older age[2], having a family history of Alzheimer's[3] and carrying the APOE-e4 gene[4]. Several studies on Alzheimer's disease and other types of dementia in different countries and continents have shown a steady increase in the incidence of dementia according to age and Alzheimer's disease is the main cause[5]. Several risk factors of dementia and Alzheimer's disease have been studied, sex is one of them. Female sex found affecting more than male. Previous prevalence surveys also found an increased risk among women[6].

1. Dr. Niloy Ranjan Roy, Indoor Medical Officer, Dept. of Neurology, DMCH, Dhaka.
2. Prof. Md. Rezaul Karim Khan, Ex. Chairman, Dept. of Neurology, BSMMU, Dhaka.
3. Dr. Md. Bahadur Ali Miah, Associate Professor, Dept. of Neurology, BSMMU, Dhaka.
4. Prof. (Dr.) Md. Rafiqul Islam, Chairman, Dept. of Neurology, BSMMU, Dhaka
5. Dr. Bipasha Majumder, MO, Dept. of Laboratory Medicine, DMCH, Dhaka.
6. Dr. Saumitra Das, Biochemist, Dept. of Biochemistry, Cumilla Medical College.
7. Mohammad Kafil Uddin, Resident (Phase- B), Dept. of Neurology, BSMMU, Dhaka.
8. Dr. Md. Azizul Haque, Medical officer. UHC, Nandigram, Bogura.
9. Dr. Imran Sarker, Assistant Professor (CC), Dept. of Clinical Neurology, NINS&H, Dhaka.

People with fewer years of formal education are at higher risk for Alzheimer's and other dementias than those with more years of formal education[7]. The effect of education on the risk of dementia and Alzheimer's disease is still controversial. Several studies have reported an increased prevalence of Alzheimer's disease in poorly educated people[8], but several case-control or population based studies failed to confirm this association[9]. A higher incidence of Alzheimer's disease was found among subjects in the North Manhattan (New York) Study who had less than 8 years of education[10]. The aims and objectives of this study were to see demographic variations among the Alzheimer's disease patients.

Methods:

This observational analytical study was conducted in Neurology ward, OPD and Dementia clinic (besides general OPD services of neurology, there are six specialized clinics are running for patients of specific neurological diseases. Dementia clinic is one of them, where only patients of dementia are evaluated and managed by neurology consultants. This clinic provides service to the patients every Thursday from 11 am to 2:30 pm. About 20-30 patients per month are getting services from this clinic. Proper registrar is maintained in the Dementia clinic for research purpose of BSMMU, Dhaka during May' 15 to February' 17. All adult consecutive patients with clinical diagnosis of Alzheimer's disease at the place of study were study population. After ethical clearance from Institutional Review Board (IRB), patients having features of AD according to revised NINCDS-ADRDA criteria[11] were selected. Informed written consent was taken from each patient or his/her attendants. After taking proper history, physical, neurological examination including MMSE were done. The cognitive impairment was assessed by MMSE[12] score (Mild 20-24, Moderate 10-19, Severe <10). Relevant investigations including MRI of brain were done to diagnose AD and rule out other causes of dementia. 45 patients were taken as cases after satisfying all the criteria for enrollment. All data were recorded in semi structured data sheet. A semi-structured questionnaire was developed in English for recording of data and MMSE sheet was translated in Bengali version.

Results:

The study included 45 Alzheimer's disease patients. Table -I shows that the mean age of AD patients was 69.20 (±11.16) years.

Table-I

Distribution of the study population by age groups (N=45).

Age (year)	Case (n=45)	Percent
45 – 54	03	6%
55 – 64	13	29%
65 – 74	15	33%
≥75	14	31%

Table-II

Distribution of the study population by gender (N=90).

Gender	Case (N-45)	Percent
Female	18	(40)
Male	27	(60)

Table -II shows that among 45 AD patients 40% were female and 60% male.

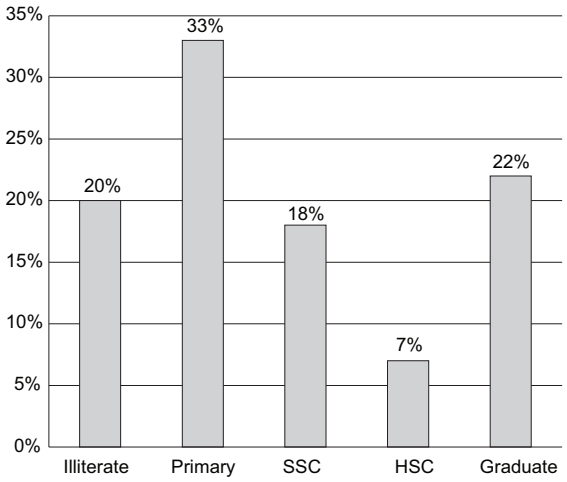

Fig.-1: *Bar diagram showing educational level of Alzheimer's disease patients* (N=45).

Figure-1 shows distribution of Alzheimer's disease patients according to educational level. Among all

the patients, a major portion of study population was taking primary education accounting 33% which is closely followed by graduation 22.% and illiteracy 20% in case group. 71% AD patients belongs to lower educational level (Illiterate up to SSC).

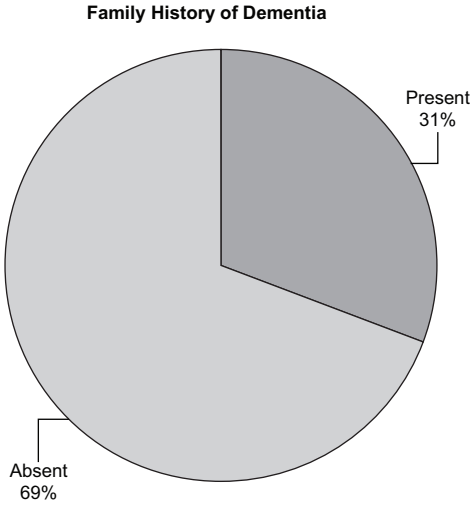

Fig.-2: *Pie chart showing Family history of dementia present in AD patients (N-45).*

Figure-2 shows that family history of dementia was present in 31% AD patients.

Table-III

Distribution of the co morbid disease of Alzheimer's disease patients (N=45).

Diseases accompanying AD patients	Number of patients
DM	31
HTN	49
CKD	29
Dyslipidaemia	47
IHD	13

Table III: shows 49 patients were hypertensive, 47 patients were suffering from dyslipidaemia, 31 patients were diabetic, 29 patients were suffering from CKD, 13 patients were suffering from IHD.

Discussion:

In this study analysis of age distribution showed that, the mean age of Alzheimer's disease patients was [69.20 (± 11.16)] years. It coincides with studies like [13,14,15] but age group seemed to be higher in comparison to this study. It might be due to lower life expectancy of peoples in our country. There was male preponderance, 60% (27) were male and 40% (18) were female. It was consistent with studies like [13, 17] but does not coincide with studies like[14,15,18,19]. In context of our country, lower proportion of female patients were enrolled in this study may be due to less preference for females for seeking medical attention. Among all the patients, a major portion of study population had the primary education accounting 33%, which is closely followed by graduation 22.% and illiteracy 20% in case group. 71% AD patients belongs to lower educational level (Illiterate upto SSC). It coincides with studies like[20, 21] where they found an association between low educational level and higher risk of developing AD. A significant number of AD patients (22%) completed graduation as because patients and their family members are more concern for seeking medical attention.

Family history of dementia was present in 31% in the AD patients. Outpatient department of neurology BSMMU runs a separate weekly dementia clinic where dementia patients attended. Most of the patients presented with moderate dementia (60%) and the rest had the severe dementia (29%) and mild dementia (11%).

Conclusion:

AD patients found more after 65 yrs. Higher rate of AD was found in older man. Lower educated people affected more than higher educated.

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Bangladesh Journal of Neuroscience 2019; Vol. 35 (1): 14-21

Risk Factors Analysis in Various Subtypes of Ischemic Stroke According to TOAST Criteria in a Tertiary Care Hospital

MOHAMMAD RH[1], ISLAM MR[2], SHAHIDULLAH M[3], RAHMAN HZ[4], REFAYET CNH[5], RASHID MB[6]

Abstract:

Background: *Stroke is the third leading cause of death in adult population throughout the world and is the most common cause of severe adult physical disability. The aim of the study is to identify the major risk factors in various subtypes of ischemic stroke according to TOAST criteria. Methods: A Cross-sectional observational study was conducted from January, 2018 to December 2018 in the department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka. All the patients of first ever ischemic stroke within 14 days diagnosed by history, clinical examination and neuroimaging (CT scan of head / MRI of brain), meeting the inclusion and exclusion criteria were included in the study. Results: Present study showed that among the 52 ischemic stroke patients mean age of the respondents was 57 ± 12.37 years with a slightly higher male predominance. Male to female ratio was 1.2:1. Dyslipidemia 44 (84.6 %) and hypertension 37 (71.2 %) were the most common risk factors, followed by obesity and overweight 33(63.5%), smoking 32 (61.5%), diabetes mellitus 29 (55.8%), family history of vascular event 27(51.9 %) and past history of vascular event 14 (26.9%). TOAST Subtype distribution of study population was large-artery atherosclerosis 18 (34.6%) followed by cardioembolism 11(21.2%), small-vessel occlusion 10(19.2%), stroke of other determined etiology 3(5.8%), and stroke of undetermined etiology 10(19.2 %) of patients. In cardioembolic subtype significant association was found with ischemic heart disease (P=0.001) and chronic rheumatic heart disease (P= <0.001). Conclusion: In this study large-artery atherosclerosis was the most common subtype, followed by cardioembolism, small vessel occlusion, stroke of undetermined etiology and stroke of other determined etiology subtypes. Dyslipidemia was found to be the most common risk factor, others were HTN, diabetes and smoking. Ischemic heart disease and rheumatic heart disease were very important cause and comorbidities of cardioembolic types of ischemic stroke.*

Key words: *Ischemic stroke, Risk factors, TOAST criteria, Subtypes.*

Introduction:

Worldwide stroke is the second most leading cause of death and the third leading cause of disability in adult[1]. Due to stroke was 5·7 million people died worldwide in 2005 and projected to rise to 7.8 million in year 2030[2]. According to GBD 2016[3], Death due to stroke in South Asia has increased from 15% to 21% and the mean global lifetime risk of stroke has increased from 22.8% in 1990 to 24.9%.

Stroke is defined by World Health Organization (WHO) as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of non traumatic vascular origin[4]. The incidence of stroke varies among various countries. Over the last forty years, the stroke incidence in low- and middle-income countries has become more than doubled.

1. Dr. Rakib Hasan Mohammad, MD (Neurology) Student, Dept. of Neurology, BSMMU, Dhaka.
2. Prof Dr. Md. Rafiqul Islam, Professor & Chairman, Dept. of Neurology, BSMMU, Dhaka.
3. Dr. Md. Shahidullah, Associate Professor, Dept. of Neurology, BSMMU, Dhaka.
4. Prof. Dr. Hasan Zahidur, Rahman, Professor, Dept. of Neurology, BSMMU, Dhaka.
5. Dr. Chowdhury Neamul Hossain Refayet Resident, Dept. of Neurology, BSMMU, Dhaka.
6. Dr. Mohammad Bazlur Rashid, MD (Neurology) student, Dept. of Neurology, BSMMU, Dhaka.

During this period stroke incidence has declined by 42% in high-income countries[5]. Stroke is the third leading cause of death in Bangladesh, and the prevalence of stroke over age 40 is 300/ 100,000[6]. In a study of hospitalized stroke patient in Bangladesh, it was found that the incidence of ischemic stroke was 61% and hemorrhagic stroke 39%[7]. Mortality due to stroke increased from 6% in 2006 to around 8.57% in year 2011[6].

The etiopathogenesis of stroke is multifactorial, with multiple modifiable and non-modifiable risk factors being associated. Findings from the interstroke study suggest that HTN, current smoking, high waist-to hip ratio (abdominal obesity), sedentary lifestyle, DM, alcohol intake, psychosocial stress and depression, cardiac causes and dyslipidemia account for about 90% risk of stroke[8]. In a hospital based cross sectional study it was found that hyperlipidemia, DM, heart disease, obesity, cigarette smoking, oral contraception use, sedentary work, and previous history of TIA were risk factors for stroke in Bangladesh[7]. Various etiologies often result in different outcome, treatment and likelihood of recurrence in ischemic strokes. Large hemispheric infarcts resulting from occlusion of the internal carotid artery or proximal middle cerebral artery has the worst prognosis[9]. Mortality is higher among patients with large-artery atherosclerotic lesions than lacunar stroke. Recurrent strokes are more common in patients with lacunar[10] and cardioembolic stroke. Anticoagulants may be prescribed to prevent recurrent cardio- embolic stroke[11]. Carotid stenting and carotid endarterectomy is useful in preventing recurrent stroke in patients with large-artery stenosis whereas aspirin and ticlopidine prevent recurrence in patients with small-artery occlusive disease more than large-artery stenosis[12,13]. In this way, determining the cause of stroke does influence the outcome and choice for management.

As the etiologies of ischemic stroke are diverse, it is difficult to include all stroke subtypes within a single classification system. The TOAST classification of subtype was introduced to produce uniformity. TOAST classification was the first classification system based on stroke mechanisms. Vascular risk factors, early and long-term recurrence and survival were found to be different among the ischemic stroke subtypes classified by TOAST[14,15].

The TOAST classification system includes five categories: 1.Large-artery atherosclerosis 2. Cardioembolism 3. Small-vessel occlusion (lacune) 4. Stroke of other determined etiology 5. Stroke of undetermined etiology (Two or more causes identified, negative evaluation and incomplete evaluation)[16]. The TOAST classification system is straightforward, valid[17] and follows a logical progression[16].

There is scanty data regarding ischemic stroke prevalence, associated risk factors, outcome prediction and treatment in various subtypes of ischemic stroke in our population. In order to find out causative mechanism of ischemic stroke, many investigations are needed which all are available in BSMMU, a tertiary care hospital. This study would be helpful for our doctors to know more about the ischemic stroke with their risk factors, subtypes, treatment and prevention in Bangladesh.

Methods:

This was a cross-section observational study held in department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from January 2018 to December 2018 with the aim to explore any variations of risk factors among different subtypes of ischemic stroke according to TOAST criteria.

After ethical clearance from Institutional Review Board (IRB), this study included 52 adult patients of ischemic stroke of either sex within two weeks of first ever attack from the Department of Neurology, BSMMU. Patients with previous history of stroke, patients with hemorrhagic stroke, venous stroke and known case of malignancy, CKD and critically ill patients were excluded from this study. Purposive non random sampling was used in selecting cases.

Informed written consent was taken from each patient or from patient's attendant (for severely ill or unconscious patient). The patients were diagnosed by history, clinical examinations and

confirmed by CT scan or MRI of Brain by a consultant neurologist.

Demographic profile including age, sex, residence, occupation, educational level, income status was recorded. Information regarding hypertension, smoking, diabetes, ischemic heart disease, valvular heart disease and other relevant history were recorded through a structured questionnaire. Height and body weight were measured to asses BMI.

The patients were assessed by diagnostic tests including cardiac imaging (echocardiography, etc.), duplex imaging of extracranial arteries, arteriography, and laboratory assessments for routine and baseline investigations like CBC, Urine RME, S. Creatinine, Blood sugar,HbA1c and Lipid profile. Special investigations like transesophgeal echocardiography, vasculitic profile, CSF study and tests for prothrombotic state were done in selected cases. For study purpose, no additional biochemical and radiological tests were done.

With all aseptic precaution, 10 ml of blood was collected. Of them 2 ml was collected in EDTA vial for CBC, 2 ml in sodium citrate vial for ESR, 4ml in sodium citrate vial for biochemical study and 2 ml in EDTA vial for HbA1c. Blood samples were mixed by repeated inversions for 5-7 times and then were sent to department of Laboratory Medicine with ice bag immediately for analysis. In department of Laboratory Medicine blood samples were processed further with centrifuge at 4000 RPM for 10 minutes for biochemical study. CBC was done by Hematology Autoanalyzer (Sysmex XN-2000/ XT4000i) and was re-checked manually. RBS, HbA1c, S. Electrolyte, S. Creatinine and Lipid profile were done by Siemens Automated Biochemistry Analyzer Dimension RXL MAX, USA. Triglyceride was measured by enzymatic (end point) method, total cholesterol by cholesterol oxidase, esterase peroxidase method, LDL-C and HDL-C by direct measure (PEG) method, HbA1c by immunoturbidimetric and blood sugar by hexokinase method. Quality control (QC) was ensured by doing updated calibration and by checking 3 level QC curve showing in the autoanalyzer. Samples were stored at 2-8ÚC if there is any delay of few hours to send the samples to laboratory. All the biochemical and hematological tests were done within 14 days of index stroke. Protective measures were taken for other investigations. Hypertension, diabetes mellitus (DM), and hyperlipidemia were diagnosed according to established criteria. A structured data collection sheet was developed in English, to collect information on demographic variables, vascular risk factors, and stroke workup, and stroke subtype using TOAST criteria.

All the data were checked and edited after collection. Descriptive analysis of all relevant variables was done by using measures of Central Tendency and Dispersion. The results were expressed as means (±SD) for continuous variables and as percentages for categorical variables. Data were expressed as number (percent) and managed by SPSS for Windows Version 22. Chi-square test of proportion was applied for significance of patients with risk factors. P-value of < 0.05 was taken as statistically significant.

Results:

Mean age of the respondents was 57 ± 12.37 years (table1=I) with a slightly higher male predominance (Fig.I). Male to female ratio was 1.2:1. Present study showed that among the 52 ischemic stroke patients dyslipidemia 44 (84.6 %) and hypertension 37 (71.2 %) were the most common risk factors, followed by obesity and overweight 33(63.5%), smoking 32 (61.5%), diabetes mellitus 29 (55.8%), family history of vascular event 27(51.9 %) and past history of vascular event 14 (26.9%) (table II).

TOAST Subtype distribution of study population was large-artery atherosclerosis 18 (34.6%) followed by cardioembolism 11(21.2%), small-vessel occlusion 10(19.2%), stroke of other determined etiology 3(5.8%), and stroke of undetermined etiology 10(19.2 %) of patients (table III). Large-artery atherosclerosis 18 (34.6%) was the most common subtype of ischemic stroke and dyslipidemia was the most common risk factor (table IV). Distribution of cardiac abnormality among the TOAST subtypes showed that the most common cause of cardioembolic stroke in the this study was ischemic

heart disease (54.5%) with P value 0.001, then CRHD (45.5%) with P value < 0.001 and DCM (27.3%) with P value 0.018. These results were statistically significant. LAA subtype had normal ECG and Echocardiography findings (100%) and SVO subtype had normal ECG (90%) and normal Echocardiography findings (100%). These results had P value < 0.05 and the results were statistically significant (table V).Mean fasting serum cholesterol (total) of the respondents was 187.88 ± 49.94 mg/dl, mean fasting serum HDL cholesterol was 38.51 ± 8.38 mg/dl, mean fasting serum LDL cholesterol was 112.56 ± 39.03 mg/dl and mean fasting serum triglyceride was 183.44 ± 107.17 mg/dl. Mean HbA1c of the respondents was 7.7 ± 2.23%.(table VI).

Table-I

Distribution of study population by age (n=52)

Age group in years	n	%
Less than or equal 35 years	4	7.7%
36 to 45 years	4	7.7%
46 to 55 years	16	30.8%
56 to 65 years	18	34.6%
Above 65 years	10	19.2%
(Mean ± SD)	57 ± 12.37	

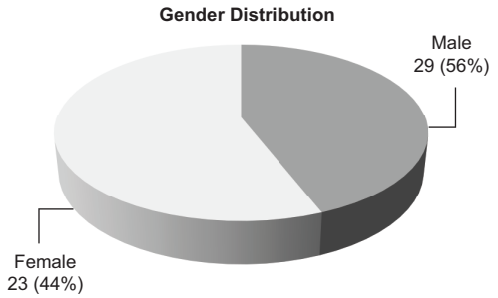

Fig.-1 (Pie chart): *Frequency of study population by gender*

Pie chart showing 29(56%) of study populations were male and 23(44%) of study populations were female.

Table-II

Common Risk factors of Ischemic Stroke

Risk factor	n	%
Diabetes	29	55.8%
Hypertension	37	71.2%
Dyslipidemia	44	84.6%
BMI(Over weight +Obese)	33	63.5%
Smoking	32	61.5%
Previous vascular event	14	26.9%
Family history	27	51.9%

Table-III

TOAST Subtype distribution of study population.

TOAST Subtype	n	%
Large artery atherosclerosis-LAA	18	34.6%
Cardioembolism-CE	11	21.2%
Small Vessel Occlusion-SVO	10	19.2%
Stroke of other determined etiology-SODE	3	5.8%
Stroke of undetermined etiology-SUDE	10	19.2%
Total	52	100%

Table-IV

Risk factors among TOAST subtypes

	LAA n=18(%)	SVO n=10(%)	CE n=11(%)	SODE n=3(%)	SUDE n=10(%)
Diabetes	10 (55.6)	6 (60)	5 (45.5)	0 (0)	8 (80)
Hypertension	14 (77.8)	7 (70)	6 (54.5)	2 (66.7)	8 (80)
Dyslipidemia	15 (83.3)	7 (70)	10 (90.9)	2 (66.7)	10 (100)
BMI(Over weight +Obese)	12 (66.7	6(60)	5(45.5)	2 (66.7)	8 (80)
Smoking	12 (66.7)	7 (70)	5 (45.5)	0 (0)	8 (80)
Previous vascular event	3 (16.7)	3 (30)	5 (45.5)	0 (0)	3 (30.0)

LAA -Large artery atherosclerosis, CE- Cardioembolism, SVO- Small Vessel Occlusion, SODE- Stroke of other determined etiology, SUDE- Stroke of undetermined etiology.

Table-V

Distribution of Cardiac Abnormality among TOAST subtypes

		TOAST SUBTYPE					
		LAA n (%)	CE n (%)	SVO n (%)	SODE n (%)	SUDE n (%)	*P Value
ECG	Normal	18 (100)	4 (36.4)	9 (90)	3 (100)	7 (70)	0.001[s]
	MI	0 (0)	5 (45.5)	1 (10)	0 (0)	3 (30)	0.017 [s]
	LVH	0 (0)	2 (18.2)	0 (0)	0 (0)	0 (0)	0.101 [ns]
	AF	0 (0)	1 (9.1)	0 (0)	0 (0)	0 (0)	0.434 [ns]
	Total	18 (100)	11 (100)	10 (100)	3 (100)	10 (100)	
Echo-cardiography	Normal	18 (100)	0 (0)	10 (100)	3 (100)	7 (70)	<0.001 [s]
	RWMA	0 (0)	6 (54.5)	0 (0)	0 (0)	3 (30)	0.001 [s]
	CRHD	0 (0)	5 (45.5)	0 (0)	0 (0)	0 (0)	<0.001 [s]
	DCM	0 (0)	3 (27.3)	0 (0)	0 (0)	0 (0)	0.018 [s]
	Total	18 (100)	11 (100)	10 (100)	3 (100)	10 (100)	

*Chi square test was done to measure the level of significance
S = significant, NS = not significant, n = Number of Patients
LAA -Large artery atherosclerosis, CE- Cardioembolism, SVO- Small Vessel Occlusion, SODE- Stroke of other determined etiology, SUDE- Stroke of undetermined etiology, MI-Myocardiac Infarction, LVH- Left Ventricular Hypertrophy, AF-Atrial Fibrillation, RWMA- Regional Wall Motion Abnormality, CRHD- Chronic Rheumatic Heart Disease, DCM- Dilated Cardiomyopathy.

Table-VI

Lipid profile and state of glycemic control of study populations

Parameter	Number of patient	Mean ± SD
Total Cholesterol (mg/dl)	52	187.88 ± 49.94
HDL Cholesterol (mg/dl)	52	38.51 ± 8.38
LDL Cholesterol (mg/dl)	52	112.56 ± 39.03
Triglyceride (TG) (mg/dl)	52	183.44 ± 107.17
HbA1c %	52	7.7 ± 2.23

Discussion:

This study was conducted with the aim to find out the risk factors among the various subtypes of ischemic stroke according to TOAST criteria in a tertiary care hospital.

A total of 52 patients were included in the study after their first ever ischemic stroke. About 85% of patients were above 45 years. Mean age of the respondents was 57 ± 12.37 years. This result is consistent with a previous study in India, where mean age was 57.1 (±1.7)[18]. Another similar study of Pakistan it mean age was found to be 63 years[19]. These results are consistent with our study. A slightly higher male predominance was observed in this study with male to female ratio of 1.2:1. This finding was similar with the other study conducted by Saha et al.,[20] with a male to female ratio of 1.6:1 and by Lange et al.,[21] who found male to female ratio 1.5:1.The lower percentage of female stroke patients indicates either a low prevalence of stroke among females or a lower access of female stroke patients to the tertiary care hospital.

In TOAST Subtype distribution of study population, the most common subtype was large-artery atherosclerosis 18 (34.6 %) followed by cardioembolism 11(21.2 %), small-vessel occlusion 10 (19.2%), stroke of other determined etiology 3 (5.8 %), and stroke of undetermined etiology 10 (19.2 %) of patients. In one study in Bangladesh large-artery atherosclerosis was 32.5 %, small-vessel occlusion was 45.3%, cardioembolism was 4.8 % and stroke of undetermined etiology was

17.2 % of patients[22]. The number of patients in small vessel occlusion stroke was small in our study because due to less severe symptoms many patients did not reach to a tertiary care hospital like BSMMU. In India Renjen et al,[18] found large-artery atherosclerosis 57.7 %, small-vessel occlusion 7.7%, cardioembolism 4.5 % and stroke of undetermined etiology 27 % of patients. In this study dyslipidemia was the most common risk factor and was found in 84.6% patients. In a study in BIRDEM, Bhowmik et al.,[22] found dyslipidemia in 93% of patients. This finding was consistent with our study. In another study Khan et al.,[23] found dyslipidemia in 32.7% of patients and Renjen et al.,[18] found dyslipidemia in 23.7% of patients. In this study a very high proportion of the stroke patients had dyslipidemia in contrast to India and Pakistan. These differences were most likely due to change in dietary habit, sedentary life style and increasing weight of our population.

Hypertension was one of the most important modifiable risk factors which was found in 37(71.2 %) patients in this study. In a recent similar type of study Bhowmik et al.,[22] found that 74.2 % of patients were hypertensive. Renjen et al.,[18] in India found it to be 56.9 % and Nadia et al.,[19] found it to be 85 %. These findings are comparable to this study.

In this study 29 (55.8 %) patients had DM. Nadia et al., 2011 of Pakistan found 49 % patients had DM which was similar with this study. Bhowmik et al.,[22] found 74.5% of patients were diabetic and the rate was higher because BIRDEM General Hospital is a tertiary care hospital in Dhaka, run by the Diabetic Association of Bangladesh.

This study found that 61.5 % patients were smoker which was similar with the findings of another study in Bangladesh[24] (61.18 %). In this study, family history of vascular event was found in 51.9 % patients and Bhowmik et al.,[22] found positive family history in 50.8 % of patients which was almost similar.

Large-artery atherosclerosis was the most common subtype where most of the patients were aged over 45 years with slight male predominance. Dyslipidemia (83.3%) and hypertension (77.8 %) were the most common risk factors, followed by smoking (66.7%), obesity (55.6%) and DM (55.6%). Renjen et al.,[18] found Hypertension in 85% cases, Smoking in 61% cases and Diabetes in 41% cases in LAA subtype. These findings are similar with present study.

Kolominsky-Rabas et al.,[25] found hypertension in 52%, diabetes in 32%, smoking in 25% and cardiac disease in 45% patients in LAA subtype. Cause of this difference may be due to ethnic, geographical and socioeconomic differences.

In small-vessel occlusion subtype dyslipidemia (70%), HTN (70%), smoking (70%), DM (60%), obesity 30% and overweight 30% are important risk factors with equal male to female ratio. Renjen et al.,[18] found coronary artery disease, hypertension, diabetes mellitus, dyslipidemia and smoking as risk factors in this group.

In our study 3 patients (5.8 %) have other determined etiology. Of them one patient was in hypercoagulable state (protein C and anti-phospholipid antibody positive), another had neurosyphilis and other had tubercular meningitis (TBM).They were non-diabetic and non-smoker and all of them were male with positive family history of stroke. Kolominsky-Rabas et al.,[25] found 2% of their patients in this group and Lange et al.,[21] found 3.1%.

In stroke of undetermined etiology subtype dyslipidemia (100%) and hypertension (80%) are the most common risk factors, followed by diabetes mellitus (80%), smoking (80%), family history of stroke (70%), obesity 40% and overweight 40%. The reason for categorizing these patients as having an undetermined etiology was two or more causes were being identified and any of which could be responsible and in a few cases evaluation was incomplete.

Distribution of cardiac abnormality among the TOAST subtypes showed that the most common cause of cardioembolic stroke in the this study was ischemic heart disease (54.5%) with P value 0.001, then chronic rheumatic heart disease (45.5%) with P value < 0.001 and dilated cardiomyopathy (27.3%) with P value 0.018. These results were statistically significant. Aquil et al.,[19] found ischemic

heart disease as most common risk factor whereas Renjen et al.,[18] found atrial fibrillation as major risk factor in CE subtype. It was also observed that -Large-artery atherosclerosis subtype had normal ECG and Echocardiography findings (100%). Small-vessel occlusion subtype had normal ECG (90%) and normal Echocardiography findings (100%). These results had P value < 0.05 and the results were statistically significant.

There are several limitations of the study. The study was done in short period with small sample size. Method of sampling was purposive, i.e. non-random sampling and study population were enrolled from only one center hence it may not represent the whole population of the country.

Conclusion:

Present study showed that the etiopathogenesis of ischemic stroke varies among different subtypes. In this study large-artery atherosclerosis was the most common subtype, followed by cardioembolism, small vessel occlusion, stroke of undetermined etiology and stroke of other determined etiology subtypes. Dyslipidemia was found to be the most common risk factor, others were HTN, diabetes and smoking. Although there were variations in distributions of risk factors among different subtypes, but most of them were not statistically significant. Ischemic heart disease and rheumatic heart disease were very important cause and comorbidities of cardioembolic types of ischemic stroke.

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Socio Demographic and Headache Characteristics of Migraine Patients in a Tertiary Care Hospital in Bangladesh

BHATTACHARJEE M[1], KARIM MR[2], HOSSAIN A[3], MONDOL G[4], BISWAS R[5]

Abstract:

Migraine is a common type of headache. After tension type headache, it is the second common cause of primary headache disorder with a female preponderance.This cross sectional study was done toassess the sociodemographic characteristics of migraine patients in Bangladeshi population and to see the characteristics of headache and associated comorbidities of migraine patients.The study was conducted in a tertiary care hospital (Mymensingh medical college) of Bangladesh.The study subjects consisted of 60 patients with migraine headache seen in neurology OPD.Mean age was 32.03± 11.74 yrs. Male female ratio was 1: 2.7.Most of them are housewives (61.6%). 22% had family history of headache. Most of the patients had severe (53.4%) and frequent (e"3 per month) headache attacks. Aura was present in 25% patients. Depressive illness was the associated comorbid condition which was found in 15% patients.

Key words: *Migraine, Socio demography, Comorbidity*

Introduction:

Migraine is a common type of headache. After tension type headache, it is the second common cause of primary headache disorder with a female preponderance. Migraine constitutes 16% of primary headache and it affects 10-20% of general population[1].Lifetime prevalence ranging between 14 and 16 %[2]. It is ranked as third highest cause of disability worldwide in both males and females under the age of 50 years[3]. It is a unilateral, recurrent, episodic headache associated with nausea and or vomiting and sensitivity to light, sound or movement. Studies have revealed that 4-6% of men, 13-18% of women are afflicted with migraine worldwide over a 1-year period[4].It usually begins in adolescence but may occur in childhood. More than 80% of cases it begins before the age of 30, and in 50% of cases before 20 years of age[5].World Health Organization declared migraine as the most disabling medical conditions experienced worldwide[6]. The indirect costs of migraine related to decreased productivity and lost days of work have been calculated to be $13 billion per year[7]. The pathophysiology of migraine is still unclear. There are few hypothesises.Clinical and experimental evidence supports the concept of abnormal intracranial and extra cranial vascular reactivity in migraine and other vascular headaches.In 2018 the Third Headache Classification Committee of International Headache Society (IHS) published a detailed classification of Headache Disorders, the 3rd edition[8]. In that edition Migraine headache is classified in six subtypes. There is evidence that the patients with migraine are often comorbid with other diseases, such as stroke, hypertension, diabetes, Bronchial Asthma, obesity and depression[9,10]. We believe that a nationwide

1. Dr. Manabendra Bhattacharjee, Associate Professor, Dept. of Neurology, Mymensingh Medical College, Mymensingh, Bangladesh
2. Dr. MD. Rezaul Karim, Registrar, Dept. of Neurology, Mymensingh Medical College hospital, Mymensingh, Bangladesh.
3. Dr. Akmal Hossain, Resident, Neurology (Phase B), Mymensingh Medical College, Mymensingh, Bangladesh
4. Dr. Gurudas Mondol, Associate Professor, Dept. of Neurology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.
5. Dr. Rajib Biswas, Junior consultant (C.C) Medicine, Saturia UHC, Manikganj, Bangladesh

epidemiological study of migraine in the general population is needed. And as a primary work, a hospital based study to asses the section of population with migraine headache and its characters would be helpful. Therefore, the aim of this study was to assess the sociodemographic characteristics of migraine patients in Bangladeshi population and to see the characteristics of headache and associated co morbidities of migraine patients.

Methods:

This cross-sectional study was carried out in the outpatient department of Neurology, Mymensingh Medical College Hospital, Bangladesh from January 2018 to Dec 2018. The patients were selected on the basis of International headache society (IHS) migraine headache criteria[8].Total sixty patients with the typical history of migraine, age above 12 years were included in this study. Headache due to other than migraine and those were refused to include in this study were excluded.The clinical features, investigation findings and relevant data were collected in a preformed data sheet from each patient. Severity of headache was assessed by visual analogue scale. Co morbid conditions were assessed by relevant history and investigations. Depression was diagnosed on the basis of DSM-IV criteria. Informed written consent was taken from each participant. The study was approved by the Institutional review board (IRB) of Mymensingh Medical College. Analysis of data was done by SPSS version 23.

Results:

This cross-sectional study was done on 60 patients attending in outpatient department of Neurology, Mymensingh Medical College Hospital with migraine fulfilling the criteria of international headache society. Sociodemographic variables and characteristics of headache were assessed. Other co-morbidities were also documented.

Table-I

Characteristics of migraine patients (n=60).

Age(Years)	Frequency (N=60)	Percentage
<20	07	11.7
20-30	27	45
31-40	10	16.7
41-50	11	18.3
>50	05	8.3
Mean± SD	32.03± 11.74	32.03± 11.74
Sex		
Male	16	26.7
Female	44	73.3
Occupation		
Housewife	37	61.6
Student	10	16.7
Business	05	08.3
Service	04	6.7
Others	04	6.7
Socioeconomic status		
Lower class	30	50
Middle class	29	48.3
Upper class	01	1.7
Family history of headache		
Present	22	36.7
Absent	38	63.3

Table-1 demonstrates the socio demographic variables. The mean age of migraine patients was 32.03 ± 11.74 years.Highest no. of patients was in age group 20 to 30 years. Regarding gender distribution, 26.7% patients were male and 73.3% were female. Male to female ratio was 1: 2.75. Maximum (61.6%) patients were housewife. 50% belongs from lower class and 48.3% were from middle class. Family history of headache was found in 36.7% patients.

Table-II

Characteristics of headache of migraineurs (n=60)

Characters	Frequency (N=60)	Percentage
Severity of headache		
Mild	04	6.6
Moderate	24	40
Severe	32	53.4
Frequency of headache		
<3 per month	18	30
≥3 per month	42	70
Location of headache		
Unilateral	50	83.3
Bilateral	10	16.7
Type of migraine		
With aura	15	25
Without aura	45	75

Table II demonstrates the headache characteristics. Quality of headache was moderate (40%) to severe (53.4%). Most of the patients (70%) had headache frequency e"3 per month. Unilateral headache in 83.3% patients and migraine with aura was present in 25% patients whereas most of the patients (75%) had migraine without aura.

Table-III

Distribution of migraine patients with various comorbid conditions (n=60).

		Frequency (n=60)	Percentage
Hypertension	Present	04	6.6
	Absent	56	93.4
IHD	Present	03	5
	Absent	57	95
Stroke	Present	02	3.3
	Absent	58	96.7
Epilepsy	Present	01	1.7
	Absent	59	98.3
Depression	Present	15	25
	Absent	45	75

Table III shows the associated comorbidities with migraine headache, Very few cases had Hypertension, Ischemic heart disease, Stroke and Epilepsy. But 25% patients had associated depression.

Discussion:

This Cross-sectionalstudy was carried out in outpatient department of Mymensingh medical college hospital, Mymensingh. Total 60 patients of migraine were studied according to selection criteria. Sociodemographic and headache characteristics were studied. Associated comorbid conditions were also assessed.

In the study 45% of the migraine patients were in the age group 20-30 years. Majority of the patients (61.7%) were in 20-40 years age group. Mean age of migraine patients was 32.03 ±.74 years. 26.7% were male and 73.3% were female. The male and female ratio were1:2.7. Similar findings were observed in a study[11] in Bangladesh in 2017 where the mean age was 33.8±8.8 years. They found 76% patients were between 21-40 years. Male: female ratio was 1:2.6. Another study[12] found nearly 79.6% patients were from 15-35 years and male: female ratio was 1:1.7.

In this study, house wives and students occupied the largest number of study subjects, 61.6% and 16.7% respectably. Hasanet al[12] found housewife 43.7% and student 28.1%. Boru et al.[13]and Hossain et al[11] also observed most of the migraine patients were house wives. Regarding socioeconomic status among migraine patient, 50% were of low income group and 48.3% were of middle class group.Only one patient from higher socioeconomic class may be due to lack of their presence in outpatient department. Stewart (2013)[14] mentioned migraine is more prevalent in low socioeconomic condition. A population based study[15] was also found Migraine is more prevalent in low socioeconomic conditions. In our study we found more or less similar patients in these two groups, may be due to small sample size and hospital based study.

Family history of headache was present in 36.7% patients. Mixed findings were observed in different studies. Boru et al.[13] reported positive family history in 33.1 % cases of migraine which is similar of this study whereas Boes et al.[16] found it in 90% of cases.

Regarding headache characteristics we found 53.4% patients had severe headache and 40% had

moderate headache. Most of the patients (70%) had headache frequency 3 or more per months and headache starts unilaterally (83.3%). Hossain[11] found 56.7% with severe headache. Gulet al[17] found average 4.08 attacks per month. In this study, migraine with aura was 25% and migraine without aura was 75% and ratio was 1:3. In previous cross sectional population study[18] the ratio was 1:5.

Migraine with associated comorbid conditions, we found very few percentage of patients with Hypertension, Ischemic heart disease, Stroke and Epilepsy. But over 15% patients had associated depression. In Buse et al study[19], they found people with migraine were significantly ($P < 0.001$) more likely to report insomnia (OR 3.79 [3.6, 4.0]), depression (OR 3.18 [3.0, 3.3]), anxiety (OR 3.18 [3.0 3.3], angina or IHD (OR 2.64 [2.4, 3.0]). Hossain[11]found 18.2% patients had Major depressive disorder and 24.2% had generalised anxiety disorders.

Limitation:

It was a hospital based study with small sample size, so complete epidemiological statistics might not been achieved what would have been assessed in a large community study.

Conclusion:

In conclusion, from this study we found migraine is more common in 20-40 years age group and females are more sufferer than males and most of them are housewives. 22% had family history of headache. Most of the patients had severe and frequent headache. Aura was present in 25% patients. Depressive illness was the associated comorbid condition which was found in 15% patients. Further large community study should be carried out for better understanding of demographic and clinical characteristics of this prevalent disorder.

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Vascular Imaging Based Subtyping of Ischemic Stroke in BSMMU

SHAHIDULLAH M[1], DEY SK[2], AHMED A[3], DAS P[4], SULTANA N[5]

Abstract:

Background: *Most strokes and stroke related death & disability happened in low and middle income countries. The clinician should be familiar with the sub typing of ischemic stroke patients and the risk factors analysis. Vascular imaging is necessary for classifying the patient. The main objective of this study was to evaluate the subtype of ischemic stroke patients and risk factor analysis of different etiology.* ***Method:*** *This is a hospital based prospective study in Bangladesh. Within the time frame of 2014 March to 2017 November; we analyzed 1978 patients of ischemic stroke within 10 days of symptom onset. Among them 877 patients have been selected for this study to whom brain imaging (CT/ MRI), vascular imaging (MRA, DSA), ECG and echocardiography have been done. We did subtyping according to TOAST criteria.* ***Results:*** *The mean age of patients was 60.5±11 years with 70.47% subjects male and 29.53% female. Within the classification of TOAST, we have found 43.87% of patients were in large artery atherosclerosis group, 23.83.% in small vessel occlusion group, 8.46% in cardiac embolism group, 19.30% in undetermined etiology group and 4.54% in other determined etiology. Among risk factors hypertension in 58.15%, DM was found in 38.42%, hypercholesterolemia in 38.88% of patients. Hypertension was significantly high in large artery atherosclerosis group.* ***Conclusion:*** *In ischemic stroke patients, large artery atherosclerosis was the most common subtype and hypertension was significant in this group.*

Keywords: *Ischemic stroke, Subtype, TOAST criteria, Risk factor, HTN*

Introduction:

Worldwide stroke is the second most common cause of death[1] and the most known cause of severe disability[2]. Strokes can be classified into ischemic and hemorrhagic types[3]. Worldwide about 69% of stroke, 71% of stroke death and 78% of DALYs lost occurred in low-income and middle-income countries. Globally there was 25% increase in incidence of people ranging from 20-64 years of age, 23% increase in prevalence in high income countries, increase mortality rate in south Asia within 1990 to 2010[4]. Prevalence rate of stroke in Bangladesh is around 0.3%[5]. Ischemic stroke is a heterogeneous disorder and there are multiple mechanisms for it[6]. Pathophysiologically ischemic stroke may occur due to thrombosis of large or small vessels, emboli from heart or artery, hypoperfusion in watershed area or border zone[7]. In western population cardioembolic stroke is the dominant cause, in India large artery atherosclerosis and in Pakistan lacunar stroke is the most common cause of ischemic stroke[8]. Among the important risk factors are uncontrolled hypertension, dyslipidaemia, diabetes mellitus, coronary artery disease, atrial fibrillation, smoking and those vary with stroke subtypes[9,10].

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification was introduced in 1993 to classify ischemic stroke according to mechanism of ischemia. It is divided into 5 groups: large artery atherosclerosis (LAA), cardikoembolism (CE), small vessel occlusion (SVO), stroke of other

1. Dr. Md. Shahidullah, Associate Professor, Department Of Neurology, BSMMU
2. Dr. Subash Kanti Dey, Associate Professor, Department Of Neurology, BSMMU
3. Dr. Anis Ahmed, Assistant Professor, Department Of Neurology, BSMMU
4. Dr. Panchanan Das, Associate Professor, Department Of Neurology, Cumilla Medical College
5. Prof. Dr. Nahid Sultana, Professor, Department Of Community Medicine, Dhaka National Medical College

determined etiology (SODE), stroke of undetrermined etiology (SUDE)[11]. In retrospective study TOAST classification had been proven as valid and reliable[12]. Many studies had been done to identify the risk factors in each sub types in different community. There is a little data regarding ischemic stroke subtypes and their risk factors in Bangladeshi people. We wanted to know the common etiology, subtypes and risk factors of each subtypes in ischemic stroke.

Methods:

This was a prospective, cross-sectional study conducted in Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka which is a tertiary care hospital and post graduate institute. We took medical data of hospitalized patients in neurology department from March 2014 to November 2018. We defined stroke according to WHO criteria as features of focal and global cererbral dysfunction that lasting for more than 24 hours with no other than vascular cause. Any ischemic stroke patients of more than 18 years of age and within 10 days of symptom onset, willing to be included were enrolled in this study. Any TIA, venous stroke or hemorrhagic stroke patients were excluded for enrollment. After clinical examination brain imaging (CT/ MRI), ECG, ehocardiography and vascular imaging (MRA/ CTA, cerebral DSA) had been advised in all patients. As financial matters have to be paid by patient himself so all patients were not able to do all investigations necessary for the sub typing of ischemic stroke. They did duplex study of neck vessels as vascular imaging but they were not included in this study. Total 1978 ischemic stroke patients were enrolled but only 677 had been selected for this study. Sub typing of ischemic stroke into 5 categories were done according to the TOAST criteria[11]: 1. Large-artery atherosclerosis – LAA, diagnosed by clinical features of cortical dysfunction and criteria of vascular imaging that is > 50% stenosis or occlusion of major artery or cortical artery; 2. Cardioembolism- CE, diagnosed by major risk factors for embolism at least one and no apparent evidence of other subtypes; 3. Small-vessel occlusion – SVO, diagnosed by clinical features of lacunar syndrome with no cortical features and lesion in brain imaging should be <1.5 cm; 4. Stroke of other determined etiology- SODE, diagnosed by other evidence of stroke risk factors as hypercoagulability, evidence of vasculitis, dissection, moya-moya found in vascular imaging; 5. Stroke of undetermined etiology- SUDE, diagnosed by when two or more causes were identified. Sub typing was done after all documents were available to the patient. Statistical analysis was performed using software SPSS for windows. Numerical data is presented as mean ± standard deviation (SD) and risk factors and sub typing are presented as percentages. Chi-square & Fisher's exact test was done to compare between qualitative data. Analysis was defined significant when p- value is <0.05.

Results:

We enrolled 1978 patients of ischemic stroke within 10 days of symptom onset. Among them 877 patients had been selected for this study to whom brain imaging (CT/ MRI), vascular imaging (MRA, DSA), ECG and echocardiography had been done. Of all 877 patients, 542 (61.78 %) were male and 335 (36.22 %) were female. The mean age of patients was 60.5 ± 11 years.

Table-I

Distribution of respondents by age and gender

Distribution of respondents by age and gender		
Age Group	Number	Percentage
<30	41	4.67%
30-40	76	8.67%
41-50	170	19.33%
51-60	257	29.33%
61-70	207	23.67%
>70	126	14.33%
Total	877	100%
By gender		
Male	618	70.47%
Female	259	29.53%
Total	877	100%

Table-II

The subtype of Ischemic Stroke

Category	Number of patients	Percentage
Large-artery atherosclerosis (LAA)	385	43.87%
Cardio-embolism (CE)	74	8.46%
Small-vessel occlusion (SVO)	209	23.83%
Stroke of other determined etiology (SODE)	40	4.54%
Stroke of undetermined etiology (SUDE)	169	19.30%
Total	877	100%

Table-III

Risk factors of different etiology

Category	Previous H/O stroke	DM	HTN	DL
LAA n= 385	53 (13.77%)	178 (46.23%)	318 (82.59%)	189 (49.09%)
CEn=74	6 (8.1%	3 (4.05%)	10 (13.51%)	9 (12.16%)
SVOn= 209	12 (5.74%)	90 (43.06%)	87 (41.62%)	77 (36.84%)
SODEn= 40	3 (7.5%)	5 (12.5%)	4 (10%)	7 (17.5%)
SUDEn= 169	17 (10.09%)	61 (36.09%)	91 (53.84%)	59 (34.92%)
Total (n=877)	94 (10.37%)	337 (38.42%)	510 (58.15%)	341 (38.88%)
p value	.962	.201	.005*	.201

Most patients (29.23%) belonged to the age group 51-60, followed by 23.67% from 61-70 age groups. A total 67.33% was above the age of 50. The most common stroke subtypes was large artery atherosclerosis LAA (n=385, 43.87%), followed by small vessel occlusion SVO (n=209, 23.83%), Stroke of undetermined etiology SUDE (n=169, 19.30%), Cardio-embolism CE (n= 74, 8.46%), Stroke of other determined etiology SODE (n=40, 4.54%).

About risk factors, hypertension was found in (n=510, 58.15%) patients followed by dyslipidaemia (n=341, 38.88%) and diabetic mellitus (n=337, 38.42%). Among the risk factors, hypertension was significantly high (n=318, 82.59% of 385) in large artery atherosclerosis group which was significant, followed by stroke of undetermined etiology (n=91, 53.84% of 169). Diabetes mellitus was also high in large artery atherosclerosis group (n=178, 46.23% of 385), followed by small vessel occlusion (n= 90, 43.06% of 209).

Discussion:

Our goal was to know the sub typing of ischemic stroke and risk factor of each subtype according to TOAST criteria. It is commonly used classification system that uses clinical feature, brain imaging findings, and vascular imaging plus some ancillary test. It is the largest single center study about sub typing of ischemic stroke in Bangladesh. 877 patients had been selected for the study among 1978 patients as rest of the patients did not get the opportunity to do basic investigations for enrollment. This study finds male predominance than female in ischemic stroke and almost two thirds of patients are above the age of 50. Renjen PN and his associates [10] found male is greater than female in India. Bhowmik NB et al.[13] found (67.7%) in Bangladesh, Shakya D and associates[14] found (51.1%) in Nepal. The finding is also similar in developed countries. A study of 1136 patients done by Caso V et al.[15] found female was lesser than (46%) male. Marija B et al.[16] found female

dominance (52%) in their study, but they took both ischemic and hemorrhagic stroke including SAH in their study. The mean age of this present study was 60.5±11 years which was comparable to the study done by Renjen PN and associates[10]. A study of 2450 patients done by Bouzidi and associates[17] found mean age was 63.2, and another of 679 patients done by Bhowmik NB et al.[13] found 60.4 years. In Nepal mean age was 63.2 years done by Shakya D and associates[14]. However in Europe Caso V et al.[15] found mean age as 72.68(±13.27).

This study finds large artery atherosclerosis (LAA) is the most common sub type as 43.67% (n=385). Kaul S et al.[18] found 37.6% as LAA in India of total 2072 patients similar to our findings. Again a study conducted in Singapore by Dev Silva et al. within South Asian population found 41% as LAA[19]. Wong LK found 47% in Thailand, Harris S et al.[20] found 59.6% in Indonesia, as LAA. Also in Chinese population the result was similar as 37.4% done by Tan YF[21]. In India study done by Shubhakaran KP[22] and Raghuvanshi S[23]showed also similar result. In contrary, Kolominsky-Raba PL et al.[24] Kang DW et al.[25] Aquil N et al.[26] found 15.3%, 16.28%, 31% ischemic stroke patients as LAA respectively. This variation could be due to ethnic origin. More cerebral DSA in our study population can be one explanation for finding more LAA as there are facility to do cerebral DSA in our department and MRA or CTA is more expensive than DSA.

In our analyses small vessel occlusion (SVO) were 23.83% which was the second most common sub type. Most of the studies done in this sub continent and south Asia found comparable result like this study. Kaul S et al[18] and Raghuvanshi S[23] in India, Zafar et al.[8] in Pakistan, Harris S et al.[20] in Indonesia found 19.9%, 17.24%, 27.7% respectively. Murthy Raju ISSVP[27] Kaul S[28] also found similar result in their study like 23.4% and 18% respectively. In developed countries the percentage of SVO is somewhat higher than in this study. Biswas M[29] in USA, Ihle-Hansen H et al.[30] in Norway, Wu CY[31] in Taiwan, De silva DA[19] in Singapore found 45.2%, 31.4%, 39.4%, 35% respectively. Aquil N[26] in Pakistan got 43% in their study that is higher than this study.

We found 8.46% of total ischemic stroke patients as cardio embolism (CE) similar to other study done in this sub continent like Aquil N et al.[26] and Syed NA et al.[32] in Pakistan as 8% and 6% rspectively, Kaul S et al[18] & Shubhakaran KP[22] in India as 10% both . Contrary, Kolominsky-Raba PL et al.[24] found CE as 27%, Kang DW et al.[25] as 40.59%, Ihle-Hansen H et al.[30] as 31.4%. This may be due to different population origin and the increased rate of cardiac disease, more extensive work like ECG, Echocardiography, Holter monitoring, Trans-esophageal echocardiography and less cerebral angiography for evaluation of ischemic stroke patients.

In this study hypertension was the most common risk factor (58.15%) followed by dyslipidaemia (38.88%) and diabetes (38.42%). This is consistent with the other srudy in this subcontinent. In Pakistan Zafar F et al.[8], Sharif F et al.[33], Taj F et al.[34] and in India Pathak A. et al.[35] found hypertension 62.7%, 71%, 78% and 65% respectively. This finding is also consistent with study in middle East, Korea as Rukn SA. et al.[36] and Kim et al.[37] found hypertension as 66% and 61.1% respectively. Zafar F. et al.[8] also found DM as 36.6% which was also comparable to this study. In this study hypertension was significantly associated in large artery atherosclerosis which is also comparable with Zafar F. et al.[8].

Conclusion:

The most common subtype of ischemic stroke in our study was large artery atherosclerosis. Hypertension was significantly high in large artery atherosclerosis group. Among male patients hypertension, diabetes, dyslipidaemia were significantly high.

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Recurrence of Ischemic Stroke Patients with Common Risk Factors

DEY SK[1], BAKSHI L[2], AHMED A[3], SHAHIDULLAH M[4], HABIB A[5], CHOWDHURY A[6], ISLAM MR[7]

Abstract:

Background: *Mortality and morbidity due to recurrent ischemic stroke is gradually increasing in Bangladesh due to gradual increase of life expectancy. Previously many studies were done to identify the risk factors of ischemic stroke. But there was scanty data about risk factors of recurrent ischemic stroke. So,it is time demanding to find out those risk factors for ischemic stroke recurrence to reduce the mortality and morbidity from recurrent ischemic stroke. The objective of the study was to determine the frequency of recurrence ischemic stroke events within one year of follow up after discharge from hospital admitted due to first ever stroke.* ***Methods:*** *This is a prospective cohort study. This study was conducted on 150 patients admitted in Neurology ward of BSMMU, presenting with first ever ischemic stroke. Patients mRS were evaluated three monthly interval for one year. Sudden onset mRS deterioration than previous one during this one year period was categorized as recurrence.* ***Results:*** *Stroke recurrence was found in 30 patients including 8 patients who died due to stroke recurrence. the most frequent age group was > 75 years representing 44.4% who developed recurrence of stroke The cumulative risk of recurrence rate was 14.7% at three months, 15.3% at six months, 17.3% at ninth months,20% at one year. Old age, Male sex, Hypertension, DM and dyslipidemia were the most common risk factors among recurrent stroke patients.* ***Conclusion: I****t was concluded that in hospital admitted patients of first ever stroke, recurrence events was more in patients of older male patients with multiple risk factors.First three months was the worst period for recurrence after index stroke.*

Key words*: stroke, recurrence, risk factors etc.*

Introduction:

Among stroke incidence and prevalence of ischemic stroke is quite high. So disability due to ischemic stroke has a greatimpact on public health in any country. In our country life expectancy gradually increasing, so incidenceof ischemic stroke and stroke recurrence is also gradually increases in population. The etiopathogenesis of stroke is multifactorial. Multiple modifiable and non-modifiable risk factors being associated. Nonmodifiable risk factors for stroke include older age, male gender, ethnicity, family history, and prior history of stroke. Modifiable risk factors include arterial hypertension, DM, dyslipidemia, heart disease, and carotid artery disease. Lifestyle factors include lack of physical activity, cigarette consumption, alcohol abuse etc. Less well-documented risk factors include blood markers (e.g., C-reactive protein), ankle-brachial blood pressure ratios, silent cerebral infarcts, white-matter hyperintensities on magnetic resonance imaging (MRI), and degree of carotid artery intima-media thickness. Findings from the INTERSTROKE study suggest that hypertension, current smoking, high waist-to-hip ratio, sedentary lifestyle, diabetes mellitus, alcohol intake,

1. Dr. Subash kanti Dey Associate professor, Department of Neurology, BSMMU, Dhaka, Bangladesh.
2. Dr. Lipy Bakshi, Assistant professor, Department of Gynae &Obs, Dhaka National Medical college, Dhaka, Bangladesh.
3. Dr. Anis ahmed, Assistant professor, Department of Neurology, BSMMU, Dhaka, Bangladesh.
4. Dr. Md. Shahidullah, Associate professor, Department of Neurology, BSMMU, Dhaka, Bangladesh.
5. Dr. Ahsan Habib , Associate professor, Department of Neurology, BSMMU, Dhaka, Bangladesh.
6. Dr. Ashish Chowdhury, Resident, Neurology, Department of Neurology, BSMMU, Dhaka, Bangladesh.
7. Prof. Dr. Md. Rafiqul Islam, Chairman and Professor, Department of Neurology, BSMMU, Dhaka, Bangladesh.

psychosocial stress and depression, cardiac causes and ratio of apolipoproteins B to A1 account for about 90% risk of stroke[1].Hypertension (63%) was the main risk factor for stroke,followed by heart disease (24%), diabetes mellitus (DM) (21%), and hyperlipidaemia (7%). A study done within 400 hospitalized stroke patients in Dhaka medical college Hospital from July to December 2007 revealed 56·25%patients had cerebral infraction. The risk factors present in the stroke cases included hypertension (58·62%) cigarette smoking (53·79%), lipid disorder (48·01%), heart diseases (25·75%), DM (20·01%), and previous history of stroke (10·61%) [2]. In another study, the risk factors for stroke were investigated in 85 young patients (aged 14 to 45 years) hospitalized at the DMCH between January 2008 and July 2009.[3]The majority (61·18%) suffered from an Ishemic stroke . The common risk factors were hypertension (60·00%), hypercholesterolaemia (38·80%), diabetes (35·20%), smoking (32·90%), premature atherosclerosis (8·20%), and oral contraceptive use (3·8%).

Stroke recurrence after initial stroke vary widely in different studies from 3 to 22% in one year[4,15]. Recurrent stroke was defined as a new cerebrovascular event that met one of the following criteria[7,12]. (1) If new neurological deficit that was clearly different from that of the index stroke, (2) if neurological deficit follow anatomical area other than index case (3) if new deficit follow stroke subtype different from that of the index stroke. Systemic causes of clinical deterioration after an initial stroke (eg, hypoxia, hypotension, hyperglycemia, infection) may worsening symptoms of index cases during follow up[16]. It must be excluded before diagnosis of recurrence event. There was no definition of early recurrence, In this study if recurrence within three months after index stroke diagnosed as early recurrence and a similar criterion had been used by other studies of early recurrence[17,18].

Many studies were done for modifiable and non-modifiable risk factors for ischemic stroke. But there was scanty data in home and abroad about risk factors for recurrent stroke. No consensus yet exists about contribution of risk factors for recurrent stroke. This study showed the effect of widely accepted stroke risk factors on recurrent stroke after first-ever ischemic infarction.

Methods:

This study was done on the first ever ischemic stroke patients admitted in the inpatient Neurology Department of BSMMU. Total 162 patients were selected for study, but due to cognitive impairment after stroke seven patients were excluded, another five patients were excluded from the study due to non-co-operative in three monthly follow up. So total 150 patients were analyzed for recurrence three months interval up to one year.All patients give follow up for recurrence by measuring mRS scale comparing with the previous status. Deterioration of any index case mRS scale than previous was recorded as recurrence.

Results :

Table-I

Distribution of the patients according to age

Age (Years)	n	Recurrence		p value
		Yes	No	
≤45	15	0 (.0)	15 (100.0)	
46-55	35	6 (17.1)	29 (82.9)	
56-65	51	11 (21.6)	40 (78.4)	
66-75	40	9 (22.5)	31 (77.5)	
>75	9	4 (44.4)	5 (55.6)	
Total	150	30 (20.0)	120 (80.0)	
Mean±SD		64.80±9.48	60.04±11.12	0.033[a]

Table I shows that the most frequent age group was > 75 years representing 44.4% who developed recurrence of stroke but 55.6% was not developed. But most of the ischemic stroke patients were 56-65 years group among them 21.6% patients developed recurrence.

Table-II

Distribution of the patients according to sex by recurrence

Sex	n	Recurrence		p value
		Yes	No	
Male	80	17 (21.2)	63 (78.8)	0.682[a]
Female	70	13 (18.6)	57 (81.4)	
Total	150	30 (20.0)	120 (80.0)	

Table II showed male patient developed more recurrence.

Table-III

Distribution of the patients according to co-morbidity/risk factors by age

Co-morbidity / risk factors	n	Age (years)					p value
		≤45	46-55	56-65	66-75	>75	
HTN							
• Yes	106	8 (7.5)	25 (23.6)	36 (34.0)	32 (30.2)	5 (4.7)	0.302[a]
• No	44	7 (15.9)	10 (22.7)	15 (34.1)	8 (18.2)	4 (9.1)	
DM							
• Yes	75	5 (6.7)	23 (30.7)	28 (37.3)	14 (18.7)	5 (6.7)	0.053[a]
• No	75	10 (13.3)	12 (16.0)	23 (30.7)	26 (34.7)	4 (5.3)	
Smoking							
• Yes	37	2 (5.4)	9 (24.3)	15 (40.5)	8 (21.6)	3 (8.1)	0.643[a]
• No	113	13 (11.5)	26 (23.0)	36 (31.9)	32 (28.3)	6 (5.3)	
Dyslipidaemia							
• Yes	69	4 (5.8)	19 (27.5)	23 (33.3)	19 (27.5)	4 (5.8)	0.511[a]
• No	81	11 (13.6)	16 (19.8)	28 (34.6)	21 (25.9)	5 (6.2)	
Family history							
• Yes	39	5 (12.8)	13 (33.3)	10 (25.6)	10 (25.6)	1 (2.6)	0.306[a]
• No	111	10 (9.0)	22 (19.8)	41 (36.9)	30 (27.0)	8 (7.2)	
AF							
• Yes	25	1 (4.0)	6 (24.0)	12 (48.0)	2 (8.0)	4 (16.0)	0.019[a]
• No	125	14 (11.2)	29 (23.2)	39 (31.2)	38 (30.4)	5 (4.0)	

Table-IV

Distribution of the patients according to co-morbidity/risk factors by recurrence

Co-morbidity/risk factors	n	Recurrence		p value
		Yes	No	
HTN				
• Yes	106	22 (20.8)	84 (79.2)	0.720[a]
• No	44	8 (18.2)	36 (81.8)	
DM				
• Yes	75	17 (22.7)	58 (77.3)	0.414[a]
• No	75	13 (17.3)	62 (82.7)	
Smoking				
• Yes	37	6 (16.2)	31 (83.8)	0.507[a]
• No	113	24 (21.2)	89 (78.8)	
Dyslipidaemia				
• Yes	69	17 (24.6)	52 (75.4)	0.190[a]
• No	81	13 (16.0)	68 (84.0)	
Family history				
• Yes	39	5 (12.8)	34 (87.2)	0.193[a]
• No	111	25 (22.5)	86 (77.5)	
IHD				
• Yes	25	6 (24.0)	19 (76.0)	0.584[a]
• No	125	24 (19.2)	101 (80.8)	

Table IV showedindex stroke patients who were hypertensive, diabetic and dyslipidemic had increased incidence of recurrence, though it was not statistically significant.

Table-V

Distribution of the patients according to multiple risk factors by recurrence

Multiple risk factors	n	Recurrence		p value
		Yes	No	
No risk factor	15	1 (6.7)	14 (93.3)	0.305[b]
One risk factor	30	5 (16.7)	25 (83.3)	0.610[a]
Two risk factors	37	11 (29.7)	26 (70.3)	0.088[a]
Three risk factors	30	7 (23.3)	23 (76.7)	0.610[a]
Four risk factors	27	5 (18.5)	22 (81.5)	0.832[a]
Five risk factors	11	1 (9.1)	10 (90.9)	0.694[b]

Table III showed most of the patient suffered from hypertension followed by DM and dyslipidemia but it was not statistically significant in any age group.

Combinations modifiable risk factors analysis showed no statistically significant contribution to recurrence of stroke.

Table-VI

Distribution of the patients according to recurrence

Recurrence	Frequency	Percent
Yes	30	20.0
No	120	80.0
Total	150	100.0

Recurrence of ischemic stroke was 20% after one year follow up.

Table-VII

Distribution of the patients according to death

Death	Frequency	Percent
Yes	8	5.3
No	142	94.7
Total	150	100.0

Case Fatality Rate = 26.7%

Table-VIII

Distribution of the patients according to cumulative recurrence

Recurrence	Frequency	Percent
Three months	22	14.7
Six months	23	15.3
Nine months	26	17.3
Twelve months	30	20.0

Most of the patients suffered from recurrence of stroke in first three months which was about 14%. After one year it was 20%.

Discussion:

In this study, stroke recurrence with multiple risk factors up to 1 year after initial ischemic stroke was estimated. The results showed that in one-year follow-up period, 20% of the patients had suffered from an ischemic stroke recurrence; moreover, 5.3% of patients died as a consequence of the recurrence. This study found that the cumulative risk of recurrence was 14.7 % at 3 months, 15.3% at 6 months 17.3% at 9 months and 20% at 1 year.Recurrence of stroke within first three months in other studies was variable. In a Japanese study , they showed it was 4.9% [19]. American heart association showed recurrence within 3 months was 7.4% [20]. This study showed recurrence rate was higher than other studies . Most probably due to inclusion of more aged patients in this study.At one year the annual risk of stroke recurrence also variable in many studies ,13% the Oxfordshire Community Stroke Project [21] 11.91% and 17.7% in china .[22, 23]4% in perth, western Australia,[24] 8% in south carolina[25]. This study showed it was 20% a little higher than other studies. In this study 8 patients (5.3%) died. Case fatality rate was 26.7% . one study showed case fatality rate was 31.8% [20]. This is also near similar to previous studies. The average age at stroke onset was 64.80 ± 9.48 years. Though most of the ischemic stroke patients were 56-65 years group, among them 21.6% patients developed recurrence. Maximum patients who developed recurrence of stroke were > 75 years age group which was 44.4%. It was not statistically significant. 21.2% male patient was developed recurrence of stroke but 18.6% female patients were developed recurrence which was also not statistically significant. This male predominant recurrence of stroke was similar with the Framingham Study[6] but not in other studies.[15]The profile of the five modifiable selected

risk factors at enrollment for these 150 stroke patients was analyzed. Only 15 (10%) patients had none of the above five risk factors. Of the remaining, 30 (20%) patients had only one risk factor, 37 (24.66%) had two risk factors, 30 (20%) had three risk factors, 27 (18%) had four risk factors, and 11 (7.33%) had all five risk factors. Most of the recurrent stroke patients has been suffering from two risk factors (29.7%) patients (Hypertension and DM) . Maximum stroke patient (74.9%) has been suffering from hypertension in this study. Previously one study showed hypertension (HTN) was associated with a higher risk of stroke recurrence [6] same result also showed in the Lehigh Valley Study[16] but it was not found in Chicago, Maryland, and Boston using the Stroke Data Bank,[7]DM was the second most common risk factors in this study. About 50% stroke patients has been suffering from DM. Similarly, patients with diabetes mellitus (DM) had an increased risk of stroke recurrence in several stroke cohorts studied by Hier et al,[7] Alter et al,[16] and Olsson et al [15]but not by Viitanen et al[14] or Broderick et al[26].

Among 150 patients, Sixty nine patient (46%) has been suffering from dyslipidemia. Among them 17 (24.7%) has recurrence of stroke. One previous study showed dyslipidaemia in recurrent stroke patients was 56%[27]. Inthis study 37patients was smoker (24.66%). Among them 16.2% patients had recurrence of stroke. One study showed 9.5% smoker developed recurrence of stroke[28].

In this study 39 patients has history of stroke in first degree relatives. Among them 12.8% had recurrence. One study showed 6.2% had family history[29]. Among 150 index stroke patients 25 patients has arrythmia.Recurrent stroke events was occurred in 24 % patients. One study showed arrthmia was present in only 5% patients who developed recurrence stroke within one year[30]. In the LVRSS Cox modeling analysis, of those cardiac conditions studied, only AF emerged as a significant predictor for stroke recurrence and 16% of patients was suffering from AF [31].

Conclusion:

Older age with multiple risk factors were more vulnerable for recurrence of ischemic stroke. First three months were the worst time for recurrence after index stroke.

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REVIEW ARTICLE

Role of Intermittent Fasting, Calorie Restriction and Autophagy in Healthy Aging: A Review of Literature

RAHMAN MS, ISLAM MR

Abstract:

Aging is a progressive process associated with decline in structure and function, hindered maintenance and repair systems, increased vulnerability to disease and death, and reduced reproductive capacity. Healthy aging can be prolonged by calorie limitation or by pharmacologic agents that mimic the effects of caloric restriction. Both fasting and the genetic inactivation of nutrient signaling converge on the induction of autophagy, a cytoplasmic recycling process that counteracts the age-associated accumulation of damaged organelles and proteins as it improves the metabolic fitness of cells. Holy Quran made it compulsory for all healthy adult Muslim to fast during Arabic month of Ramadan from early dawn to dusk. Believers of other religions also have the tradition of fasting as religious rituals in different way. The importance offasting and the autophagy process was highlighted very recently by Prof. Yoshinori Ohsumi, a Noble prize winner in medicine for his pioneering studies revealing the mechanisms of autophagy in baker's yeast 30 years ago. Here we made literature search to review experimental findings on intermittent fasting (IF) and autophagy that influences the major nutrient and growth-related signaling pathways as well as the up regulation of anti-aging pathways.

Keywords: *Aging, Fasting, Autophagy etc.*

Introduction:

Aging of population is a global public health challenge with significant implications on health care needs, as well as social burden especially to low resource countries. There is much flexibility in successful aging, but meeting the challenges will require advance planning and preparation. The extents to which research can find solutions that reduce physical and cognitive disability at older ages will determine how to cope with this fundamental transformation[1]. Successful treatment of non-communicable diseases have led to rapidly increasing number of older people, often encumbered with age-related disorders that are predicted to overwhelm health care systems[2]. Achieving healthy aging is a challenge and calorie restrictions are showing optimism in this aspect.

Autophagy and calorie restriction (CR)

Autophagy is a lysosomal degradation process or and protective housekeeping mechanism to eliminate damaged organelles, long-lived misfolded proteins and invading pathogens. Autophagy functions to recycle building blocks and energy for cellular renovation and homeostasis, allowing cells to adapt to stress. Modulation of autophagy is a potential therapeutic target for a diverse range of diseases, including metabolic conditions, neurodegenerative diseases, cancers and infectious diseases. Among inducers of autophagy, fasting and CR are the most potent non-genetic autophagy stimulators. The objective was to weigh the evidence relating the effect of CR or fasting on autophagy promotion. The evidence overwhelmingly suggests that autophagy is induced in a wide variety of tissues and organs in response to food deprivation[3].

1. Professor Dr. Md. Shahidur Rahman, Professor, Dept. of Physical Medicine and Rehabilitation , Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
2. Professor Dr. Md. Rafiqul Islam, Professor & Chairman, Dept. of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Autophagy is strongly activated by starvation conditions characterized by low levels of glucose or amino acids. When glucose levels are high, ATP is converted into cAMP and is itself further degraded into AMP. As such, a high AMP: ATP ratio reflect a high glucose level; while a reduced AMP:ATP ratio is typical of starvation conditions when glucose levels are low[4]. Autophagy functions essentially as an adaptive response to stress, particularly in the condition of nutrient deprivation, allowing for cell and organism survival. When nutrient resources are restricted, cells are able to break down and reprocess all sorts of macromolecules including proteins, lipids, and carbohydrates which can then be reused as essential building blocks for the synthesis of new macromolecules and the production of energy [5]. Autophagy facilitates the disposal of supernumerary or damaged proteins and organelles before they become toxic to the cell. A broad range of studies has revealed that basal autophagy decline is often associated with pathologies such as neurodegeneration, cancer and inflammation[6-9].

Transcriptomics

Malfunction of autophagy causes protein aggregation and neurodegeneration. Lipinski and colleagues investigated the transcriptional level alterations between healthy aging and Alzheimer disease (AD), and they found up-regulated autophagy in brain samples from AD patients compared to normal brain samples. Based on these observations, it was suggested that the up-regulated autophagy signatures in the AD patients could be a compensatory mechanism in order to remove the accumulated protein aggregates[10].

Besides its importance in neuronal functions, autophagy also influences the identity and function of myeloid cells as well. Huang et al. examined how the expression pattern of autophagy genes is changing when myeloid cells differentiate to monocytic and granulocytic cells. Based on the analysis of the temporal gene expression data using a standard clustering algorithm, 22 autophagy genes were found to be significantly altered during the monocytic and granulocytic differentiation process of myeloid progenitors into monocytes and granulocytes[11].

Metabolomics and lipidomics

Metabolomics is a recently emerging field aimed at the systemic profiling of the metabolites, which are the small molecule, intermediates and products of metabolism. Studies of the metabolome are based on two key techniques: nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry (MS)[12] . Because autophagy is tightly associated with the cell stress status, it is not surprising that autophagy-related metabolomes will be subject to changes depending on the nature of the stresses happening in the cells[4]. Lipidomics is a sub-category of metabolomics that focuses on the identification and quantification of cellular lipids. While it has been described that changes in the cellular level of ceramides, a family of lipids can affect autophagy, little is known about the regulation of these lipids by autophagy itself. A recently published study by Alexaki and colleagues sought to evaluate the implication of autophagy in the regulation of ceramides in the liver, as autophagy is essential in this organ to maintain homeostasis and prevent metabolic diseases[13].

Autophagy and cancer, regression of tumor: Cancer usually depends on high glucose level, Lashinger and colleagues have used a mouse model system to investigate the effect of caloric restriction and autophagy on the development of RAS (oncogene) driventumors. It has been shown that combining autophagy blockade and caloric restriction was sufficient to reduce the tumor volume significantly[14]. Observations made by Gaglio et al. found that blocking autophagy using the inhibitor chloroquine caused massive cell death of RAS cancer cells in vitro. However, using chloroquine in vivo did not produce any notable effect on highly aggressive RAS xenografts. Changes in the metabolome of the tumors were observed after treatment, suggesting that RAS-driven tumors have the ability to adapt to environmental modifications and metabolic stress using metabolic rewiring and alternative pathways[15]. The connections between cancer and autophagy is a growing research area. While on one hand autophagy suppresses tumorogenesis, cancer cells also activate the process to avoid the stress and up-regulate growth and tumor aggression [16].

Autophagy strongly influences cancer so that modulation of this process has been identified as a potential target for cancer therapy[17].Omics data integration is widely used to investigate the genomic events and their interactions, as well as the potential regulatory mechanisms affected in cancer[18]. To fill the gap in the number of autophagy inhibitors and potential therapeutic agents, Peppard and collaborators designed a phenotypic, cell image-based assay for small molecules that affects the accumulation of autophagosomes in starved cells expressing GFP-LC3 (green flurescent protein light chain 3)[19].

Calorie Restrictions and Intermittent fasting (IF)

Calorie restrictions mean reduced food intake and intermittent fasting means food intake at prong interval. This kind of food habit imparts many benefits in model organisms. CR also promotes stress resistance and metabolic fitness. Emerging data in experimental models and in humans indicate that these benefits occur rapidly upon initiation of CR, suggesting potential clinical relevance[20]. IF regimens that induce the metabolic switch have the potential to improve body composition in overweight individuals. Moreover, IF regimens also induce the coordinated activation of signaling pathways that optimize physiological function, enhance performance, and slow aging and disease processes. Future randomized controlled IF trials should use biomarkers of the metabolic switch as a measure of compliance and the magnitude of negative energy balance during the fasting period[21]. In recent studies conducted in overweight humans, caloric restriction has been shown to improve a number of health outcomes including reducing several cardiac risk factors[22, 23,24] improving insulin-sensitivity and enhancing mitochondrial function[25].

Several different biological mechanisms may account for the increase in health span and longevity observed in response to caloric restriction in preclinical models. For example, aging is characterized by an exponential increase of oxidatively damaged proteins, and caloric restriction has been found to down regulate the expression of genes involved in oxidative stress and ameliorate oxidative damage in several different tissues[26,27,28,29,30,31]. Additional biological changes associated with caloric restriction that may contribute to the observed increases in health span and longevity include enhanced cellular quality control through autophagy, improved function of the ubiquitin-proteosome system (UPS: removal damaged proteins), and the maintenance of a healthy population of mitochondria through biogenesis (generation of new mitochondria)[32, 33, 27, 28, 34, 35, 36]. One alternative dietary approach that may produce similar biological changes as caloric restriction that has received increasing interest from the scientific community is intermittent fasting. In contrast to traditional caloric restriction paradigms, food is not consumed during designated fasting time periods but is typically not restricted during designated feeding time periods. The length of the fasting time period can also vary but is frequently several continuous hours. Evidence that this approach may have beneficial effects on longevity first appeared several decade ago[37]. Since this time, a growing body of literature suggests that intermittent fasting regimens can trigger similar biological pathways as caloric restriction which can result in a host of beneficial biological effects including increased circulation and cardiovascular disease protection, and modulation of reactive oxygen species and inflammatory cytokines[38].

A growing body of evidence indicates that intermittent fasting regimens in particular can trigger similar biological pathways as caloric restriction. For this reason, there is increasing scientific interest in further exploring the biological and metabolic effects of intermittent fasting periods, as well as whether long-term compliance may be improved by this type of dietary approach[39]. During fasting, cells activate pathways that enhance intrinsic defenses against oxidative and metabolic stress and those that remove or repair damaged molecules. The extension of both median and maximum lifespan and the suppression of age-related diseases in laboratory animals by reduced food intake, i.e., calorie restriction (CR) are regarded as hallmarks of CR's anti-aging action. The diverse efficacy of CR to counteract aging

effects and its experimental reproducibility has made it the gold standard of many aging intervention studies of recent years. Advances in CR research on non-human primates and recent endeavors using human subjects offer a promising outlook for CR's beneficial effects in healthy human aging[40]. Restriction of the daily food intake results in weight loss, which is also, associated with better health outcomes including controlling lipid profiles, blood pressures, improving insulin sensitivity. Based on the qualitative analysis, intermittent fasting was found to be efficient in reducing weight, irrespective of the body mass index[41]. The peripheral nervous system (PNS) comprises of an extensive network of connections that convey information between the central nervous system (CNS) and peripheral organs. Long myelinated nerve fibers are particularly susceptible to age-related changes, as maintenance of the insulating glial membrane requires extensive synthesis and processing of many proteins. In rodent models, peripheral demyelination caused by genetic risk factors or by normal aging are attenuated by intermittent fasting (IF) or calorie restriction (CR)supporting a role for dietary intervention in preserving neural function[42].

Among the several approaches to interrupt aging processes, calorie restriction (CR) has been shown to recover and/or slow age-related functional declines in various organs, including the eye[43,44]. Exercise opposes deleterious effects of secondary aging by preventing the decline in mitochondrial respiration, mitigating aging-related loss of muscle mass and enhancing insulin sensitivity.[45]Preclinical studies and clinical trials have shown that intermittent fasting has broad-spectrum benefits for many health conditions, such as obesity, diabetes mellitus, cardiovascular disease, cancers, and neurologic disorders. After nearly a century of research on caloric restriction in animals, the overall conclusion was that reduced food intake robustly increases the life span. Studies of the mechanisms of caloric restriction and intermittent fasting in animal models have led to the development and testing of pharmacologic interventions that mimic the health and disease-modifying benefits of intermittent fasting. Available data from animal models suggests that the safety and efficacy of such pharmacological approaches are likely to be inferior to those of intermittent fasting[46].

Conclusions

An important objective for autophagy research in forthcoming years will be the identification of causal connections between autophagy and aging. We surmise that this goal will be facilitated by the identification of specific, highly potent pharmacologic activators or inhibitors of autophagy, as well as by the generation of sophisticated mouse models in which autophagy can be genetically switched on and off at will, in a spatially and temporarily controlled fashion. It will be necessary to assess which potential autophagy inducers are effective and applicable to humans. Recent research has indicated roles for autophagy in an increasing number of pathologies, from bacterial and viral infections to cancer, and more recently in neurodegenerative and other age-related diseases. Research also shows, caloric restriction is the most effective strategy to induce autophagy, as it activates multiple regulatory pathways. Despite the evidence for the health benefits of intermittent fasting and its applicability in many diseases, there are impediments to the widespread adoption of these eating patterns in the community and by patients. First, a diet of three meals with snacks every day is so ingrained in our culture that a change in this eating pattern will rarely be contemplated by patients or doctors.

The abundance of food and extensive marketing in developed nations are also major hurdles to be overcome. Second, on switching to an intermittent fasting regimen, many people will experience hunger, irritability, and a reduced ability to concentrate during periods of food restriction. If opulent understands the benefits of fasting they can donate their surplus food to the poverty perished people of low resource countries Muslims are habituated to fast as religious rituals and enjoying the benefits of healthy aging for thousands of years.

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CASE REPORTS

Focal Cortical Dysplasia as Cause of Refractory Epilepsy- A Case Report

SAHA S[1], MUZAHID MAA[2], CHOWDHURY A[3], HASAN M[4], ROY U[5], KABIR MS[6], ISLAM MR[7]

Abstract:

Focal Cortical Dysplasia (FCD) is one of the most common causes of refractory epilepsy in children as well as adult where malformed cortical development occurs resulting from abnormal neuronal migration due to both genetic and acquired factors. Herein, a 22-year-old male presented with recurrent secondary generalized tonic seizure with aura since childhood. Despite adequate anti-epileptic medications with good compliance the seizure was uncontrolled. As a cause, Type II FCD was diagnosed by specific neuroimaging findings supported by EEG abnormalities. Till now in refractory epilepsy FCD is rarely diagnosed but there remains a good hope of cure by surgical intervention.

Key Words: *Focal Cortical Dysplasia, Refractory Epilepsy*

Introduction:

Focal Cortical Dysplasia (FCD) is a neuronal migration disorder resulting malformed cortical development[1]. The current definition of FCD comprises presumed developmental abnormality of cortical plate, abnormal cytoarchitexture, preservation of gyral pattern, restricted in extent and manifesting with clinical seizure[2]. Both genetic and acquired factors are responsible in pathogenesis of FCD. Genetic factors involve both somatic (TSC2) and germline (DEPDC5 and NPRL3) mutation but familial cases are exceptionally reported. Recently genetic abnormality has been found in mTOR pathway[3]. Some authors also suggested TSC1, characteristics for tuberous sclerosis, is also involved as FCD may constitute a form of tuberous sclerosis without extracerebral menifestation[4, 5]. Proteins of Wnt and Notch signaling pathway, responsible for normal neuronal migration, are also found to be involved[6]. Several experimental study indicates that irradiation and methylazoxymethanol may cause DNA damage resulting FCD[7]. FCD was first detected in 1971 by Taylor and colleagues. Since then several classifications were proposed – from Taylor et al. in1971 to Palmini classification made by Blumcke in 2011[1]. According to revised 2011 ILAE classification FCD is of three types by their neuropathological feature. FCD Type I refers to isolated lesions, which present either as radial (FCD Type Ia) or tangential (FCD Type Ib) dyslamination of the cortex, that may be identified in one or multiple lobes of the brain, FCD Type II is an isolated lesion characterized by cortical dyslamination and dysmorphic neurons without (Type IIa) or with balloon cells (Type IIb), FCD Type III describes FCD that occurs in combination with hippocampal sclerosis (FCD Type IIIa), with glioneuronal tumors (FCD Type IIIb), adjacent to vascular malformations (FCD Type IIIc) or in association with lesions acquired in early life, such as a previous ischemic injury (FCD Type IIId)[3]. Epilepsy is the core manifestation of FCD which is usually drug resistant sometimes associated with

1. Dr. Sujan Saha, MD Phase B Resident, Dept of Neurology, BSMMU
2. Dr. Md. Abdullah Al Muzahid, MD Phase B Resident, Dept of Neurology, BSMMU
3. Dr. Ashish Chowdhury, MD Phase B Resident, Dept of Neurology, BSMMU
4. Dr. Mehedi Hasan, MD Phase B Resident, Dept of Neurology, BSMMU
5. Dr. Uttam Roy, MD Phase B Resident, Dept of Neurology, BSMMU
6. Dr. Md. Suman Kabir, MD Phase B Resident, Dept of Neurology, BSMMU
7. Prof. Dr. Md. Rafiqul Islam, Professor and Chairman, Dept of Neurology, BSMMU

mental retardation. Usually no significant neurological deficit occurs despite large area of cortical involvement by a lesion. Symptoms appear at any age but FCD type II manifest earlier onset comparing to type I[8, 9]. FCD type I is related to temporal lobe seizure[10, 11] and in FCD type II multilobar lesions are found often with extratemporal location and mainly in frontal lobe[9, 12]. Neuroimaging and EEG recording are two mainstay of lab-diagnostic procedures. The characteristic MRI find-ings are cortical thickening, blurring of white matter–gray matter junction, altered signal from white matter with or without the penetration through cortex (transm-antel sign), altered signal from gray matter, abnormal sul-cal or gyral pattern and segmental and/or lobar hypoplasia/atrophy[1, 13, 14]. The presence of focal epileptiform discharge is the most characteristic feature of the scalp EEG[3]. As Epilepsy in FCD is usually medically intractable surgical intervention appears to be next therapeutic procedure[1].

Case report

The patient, a 22-year-old right handed Bangladeshi male, is the only issue of nonconsanguineous healthy parents and presented with recurrent generalized seizure since 10 years of age. The seizure was sudden in onset, generalized tonic in nature followed by versive neck movement towards the left with history of frequent fall. During seizure he also haduprolling of eyeball, occasional drooling of saliva, bladder incontinence, tongue biting and frequent injury to different body parts due to fall. The episodes were stereotyped, occurring in both awake and sleep, persisting for about 3-5 minute with post ictal confusion, amnesia and drowsiness for about 1-2 hours. On query, patient also gave history of stereotyped aura in the form of rotatory movement of visual field for about 5 minute before the episodes.

He had no history of asphyxia or trauma during birth and neonatal infection or convulsion. Pregnancy period of his mother was also uneventful. His milestone of development was normal with good school performance. But he discontinued due to repeated attacks and injury in school. He had no headache, focal weakness, speech and visual disturbance, disorder of balance, involuntary movement, any positive sensory phenomenon except visual aura with normal intelligence, cognition and memory.

Initially seizure frequency was 5-6 episodes in a month without medication. Then Sodium Valproate was added and dose was increased gradually to 1400 mg/day with a frequency 2-3 episodes per month.

But due to weight gain and extreme tiredness dose was reduced gradually to 1000 mg/day and Carbamazepine was added. With Sodium Valproate 1000mg/day and Carbamazepine 800 mg/day frequency of seizure was 1-2 episodes/ month with good compliance. He was no significant family history of illness. He was immunized as per EPI schedule.

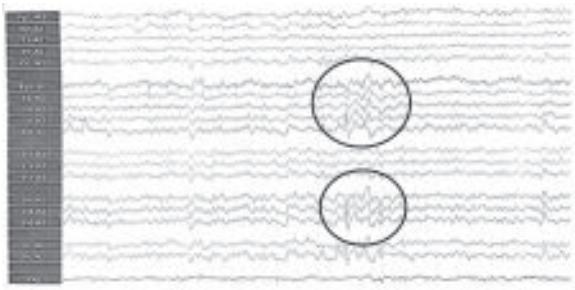

Fig.-1

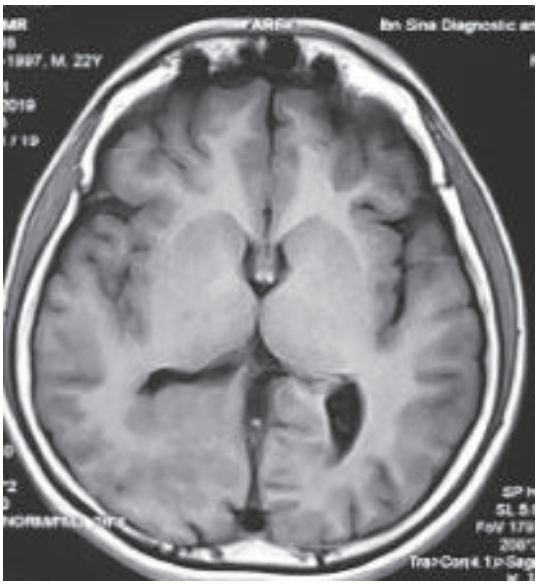

Fig.-2

General examination was normal with no abnormal cutaneous manifestation. Higher cerebral functions including speech and all cranial nerves including fundus were normal. Muscle power of upper and lower limbs both proximally and distally was MRC grade 5. All tendon and superficial reflexes including planter response were normal. All modalities of sensations were intact and there was no sign of cerebellar dysfunction.

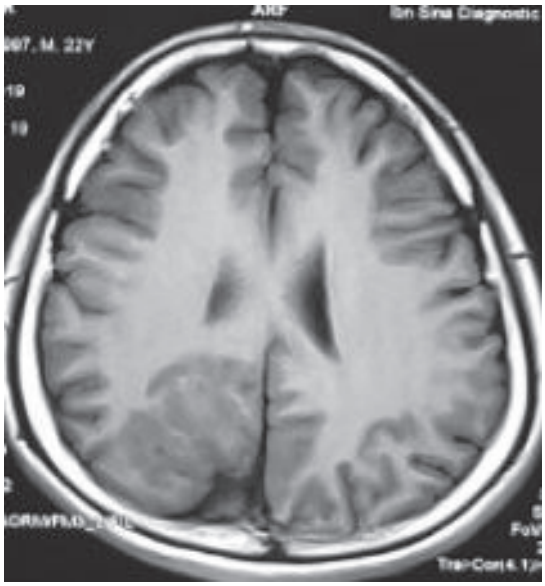

Fig.-3

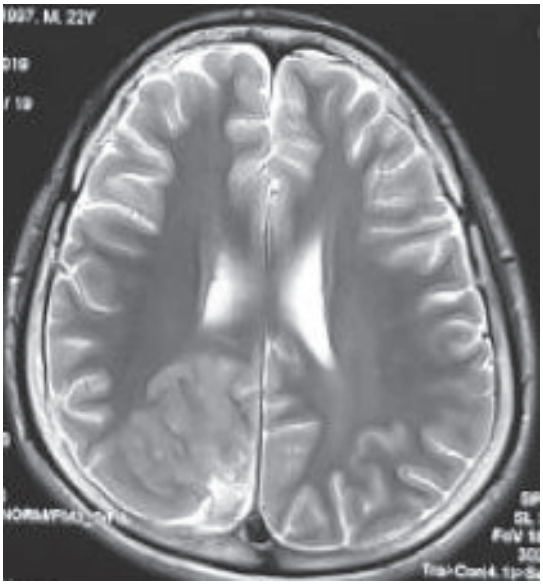

Fig.-4

Investigations revealed normal CBC, renal function, liver function, S. Electrolytes including Calcium and Magnesium. About five years ago MRI of brain and EEG were done but patient lost the document. But according to party the reports were normal. So, we decided to do MRI of brain (Epilepsy protocol) and 3 hours video assisted EEG. Neuroimaging showed FCD in right parieto-occipital region and EEG showed focal spikes and slow waves in right temporo-parieto-occipital region with secondary generalization. Then Neurosurgical consultation was taken for surgical intervention but patient denied to do the surgery.

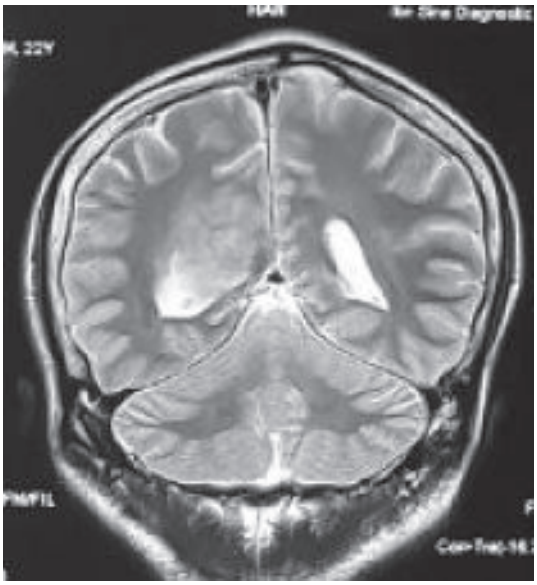

Fig.-5

Discussion:

FCD is considered to be the most common cause of medically refractory epilepsy in children and second or third common cause of medically intractable epilepsy in adults[1]. Wide variation of seizure types can occur in FCD like focal, focal onset with secondary generalization, atypical absence, atonic, tonic, tonic-clonic, epileptic spasm, generalized or focal status epilepticus. Onset of seizure occurs usually in childhood and seizure type may change over time[3].Seizure type in our patient was focal onset with secondary generalization.

Regarding EEG background may be normal or may show focal slowing. In epileptic spasm background

may show widespread slowing or hypsarrhythmia. Interictal EEG may be normal or may show focal spikes and waves or polyspikes[3]. In our patient there was focal spikes and slow waves in right temporo-parieto-occipital region (Fig: 1) with secondary generalization.

MRI of brain if abnormal may differentiate between Type I and Type II FCD. In Type I FCD lobar hypoplasia (mainly temporal lobe is involved along with hippocampal atrophty), blurring of Gray Matter/ White Matter (GM/WM) junction (less prominent than Type II), abnormal gyral pattern, subcortical white matter T2 hyperintensity or T1 hypointensity are found. In Type II FCD there are cortical thickening, marked blurring of GM/WM junction, white matter T1 hypointensity and T2 hyperintensity which may extend towards ventricle (Transmantle sign). Transmantle sign is very specific for Type II FCD and here extra temporal involvement is more common[1]. In our patient MRI of brain is suggestive of Type II FCD as evidenced by cortical thickening (Fig: A, broad arrow), marked blurring of GM/WM junction (Fig: 2, narrow arrow), white matter T1 hypointensity (Fig: 3) and T2 hyperintensity (Fig: 4) in subcortical white matter, Transmantle sign (Fig: 5) in right parieto-occipital region.

Seizure is invariably medically intractable. Our patient also experienced 1-2 episodes per month despite use of maximum tolerable dose of Sodium Valproate and Carbamazepine. So, surgical resection appeared to be next preferable therapeutic intervention. In this case Type II FCD (75%) has better seizure-free outcome than Type I FCD (20%-43%)[2]. Complete resection of cortical abnormality is crucial for seizure-free outcome but removal of cortical rather than white matter component is critical. In case of subtotal resection seizure relapse in 30% cases only within 6 months of surgery[13, 14]. So, expert neurosurgical approach is mandatory with variety of neuroimaging and EEG guidance to determine the specific focus.

Conclusion:

FCD is considered to be one of most common causes of medically intractable epilepsy not only in children but also in adult. But it is rarely diagnosed in spite of advancement in neuroimaging and EEG. In case of intractable epilepsy despite normal conventional MRI of brain and EEG we should perform, if possible, advanced neuroimaging technique (3T MRI, DTI, fMRI, FDG-PET) and increased number of electrodes in EEG to detect FCD as there is a good hope of cure by surgical intervention. Also further studies of epileptogenesis in FCD may help to develop new pharmacological era.

Conflict of interests:

The authors declare that they have no conflict of interest.

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Bangladesh Journal of Neuroscience 2019; Vol. 35 (1): 51-56

Progressive Limb Weakness in A Young Man: A Case Report of POEMS Syndrome

CHOWDHURY A[1], SAHA S[2], AL MUZAHID MA[3], ROY U[4], KABIR S[5], AGARWALLA AK[6], REZA S[7], SARKER I[8] ,ISLAM MR[8]

Abstract:

Polyneuropathy is an initial presentation and essential feature of POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome. Neuropathy is typically distal, symmetric and slowly progressive with demyelinating changes. After a gradual proximal spread, it usually results in severe muscle weakness and functional disabilities. In the present report, we describe a 40-year-old diabetic male presented with gradually progressive weakness of both lower limbs for 1 year followed by the involvement of both upper limbs for the last 3 months. On examination hyperpigmentation, lymphadenopathy, gynecomastia, anasarca, hepatomegaly, bilateral optic disc swelling, sensory-motor polyneuropathy was found. Laboratory findings showed IgG lambda monoclonal gammopathy, raised VEGF, sensory-motor demyelinating and axonal polyneuropathy. All findings were consistent with POEMS syndrome. The patient was treated with lenalidomide and dexamethasone cyclical therapy with some clinical improvement.

Keywords: *POEMS syndrome, Progressive limb weakness, Polyneuropathy, VEGF*

Introduction:

It is a rare, chronic, multisystemic, paraneoplastic disorder that occurs in the setting of plasma cell dyscrasia characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder and skin change[1-4]. The acronym, which was first coined by Bardwick in 1980[1]. However, this symptom complex is known with other names known as Osteosclerotic Myeloma, Takatsaki disease, Crow-Fukase syndrome. The real mechanism involved in the pathogenesis of POEMS syndrome is still unknown, but cytokines may play a major role[9,10]. Plasma and serum levels of VEGF are markedly increased in patients with POEMS and correlate with the activity of the disease[6,7].

The POEMS acronym refers to several essential features of this syndrome. However, not all features within the acronym are required to make a diagnosis and additional important features are not included in the acronym[4]. For a strict diagnosis of POEMS syndrome, 2 mandate criteria of polyneuropathy and monoclonal plasma cell disorder must be present. Additional requirements for the POEMS diagnosis include at least 1 other major criterion of the sclerotic bone lesion, VEGF elevation or Castleman disease, and at least 1 minor criterion of organomegaly (hepatomegaly, splenomegaly and lymphadenopathy), endocrinopathy (hypogonadism, hyper-estrogenemia, hypoparathyroidism etc), skin

1. Dr. Ashish Chowdhury, Phase B Resident, Dept. of Neurology, BSMMU, Dhaka
2. Dr. Sujan Saha, Phase B Resident, Dept. of Neurology, BSMMU, Dhaka
3. Dr. Md. Abdullah Al Muzahid, Phase B Resident, Dept. of Neurology, BSMMU, Dhaka
4. Dr. Uttam Roy, Phase B Resident, Dept. of Neurology, BSMMU, Dhaka
5. Dr. Md. Suman Kabir, Phase B Resident, Dept. of Neurology, BSMMU, Dhaka
6. Dr. Ajay Kumar Agarwalla, Assistant Register, Dept. of Neurology, SSMCH, Dhaka
7. Dr. Samim Reza, Phase B Resident, Dept. of Haematology, BSMMU, Dhaka
8. Dr. Imran Sarker, Assistant Professor(CC), Dept. of Clinical Neurology, NINS&H, Dhaka
9. Prof. Dr. Md. Rafiqul Islam, Professor and Chairman, Dept. of Neurology, BSMMU, Dhaka

change, edema, polycythemia/thrombocytosis or papilledema[2,4].

The diagnosis of POEMS syndrome is made based on a composite of clinical and laboratory features. It is a rare disorder with a reported prevalence of approximately 0.3 per 100,000 [3]. The peak incidence of the POEMS syndrome is in the fifth and sixth decades of life, unlike multiple myeloma (MM), which has a peak incidence in the seventh and eighth decades[4]. A male preponderance also observed with POEMS[4]. A good history and physical examination followed by appropriate testing, most notably radiographic assessment of bones, measurement of vascular endothelial growth factor (VEGF), careful analysis of a bone marrow biopsy can differentiate this syndrome from other conditions like CIDP, monoclonal gammopathy of undetermined significance (MGUS), neuropathy, immunoglobulin light chain amyloid neuropathy. There is a Castle- man variant of POEMS syndrome that does not have a clonal plasma cell proliferative disorder underlying but has many of the other paraneoplastic features.[12-14]

Peripheral polyneuropathy in POEMS is usually symmetrical ascending sensorimotor polyneuropathy. The polyneuropathy usually begins with sensory changes in the lower extremities, then progressing to the motor deficit. As demonstrated in this case report, the course of polyneuropathy is usually a steady progression, at times more rapidly, until appropriate treatment is given to the underlying plasmacytoma[4].

Case Report:

A 40-year-old man, college teacher, nonsmoker, non-alcoholic, normotensive but diabetic healing from Cumilla was admitted into the department of neurology, BSMMU, Dhaka, Bangladesh. He was presented with the complaints of weakness of both lower limbs for the last 1 year and swelling of both legs for the last 3 months. According to the patient, he was reasonably well about 1 year back, then he developed weakness in both lower limb, which was insidious onset, gradually progressive, symmetrical and involved distal parts. Initially, the symptom was mild, but for the last 3 months weakness became so severe that the patient could not walk or even stand without help from others and it gradually involved the upper limbs also. on a query, he also complained about tingling and numbness of all four limbs for the same duration. He also noticed swelling of both feet for the last 3 months and some painless lump on his left side of the neck for around 9 months. He denied any history of fever, anorexia, cough, breathlessness, weight loss, night sweat, body aches, joint pain, skin rash, jaundice, scanty micturition, headache, visual disturbance or dizziness or difficulty in standing from sitting. He was not a strict vegan and his bowel and bladder habit was normal. He is diabetic for the last 10 years, initially on OHA but now on insulin. For his illness, he visited several physicians in Bangladesh and abroad. He underwent several biochemical, hematological and neurological investigations and treated accordingly but no clinical improvement occurred. No significant drug history. But for his illness, he took Pregabalin, Multivitamin and Vit-B1, 6, 12. He is blessed with 3 children. He had 8 siblings. His parents were alive. All were in good health with no significant symptoms.

At the time of presentation to us, he was alert with a body built below average. Vitals were within normal limits with no anemia, jaundice, clubbing, thyromegaly, bony tenderness. But the patient had some hyperpigmentation lesions in different parts of body. The patient had firm, discrete, multiple, non-tender, left anterior cervical lymphadenopathy. Gynecomastia and bi-pedal pitting edema were also present. Regarding neurological examinations higher cerebral function including speech was normal. All cranial nerves were intact except fundoscopy revealed bilateral optic disc swelling. Motor examination revealed bilateral symmetrical wasting of both lower limbs, no fasciculation but bilateral foot drop was present. Muscle tone was reduced in all four limbs. Muscle power was MRC grade 4 in upper limbs both proximally and distally. In the lower limbs muscle power was MRC grade 3 proximally and MRC grade 2 distally. All deep tendon reflexes were diminished, plantar response was bilateral flexor, gait could not be evaluated due to weakness. Cerebellar function was intact. Hyperesthesia in gloves and stocking pattern was present in both upper and lower limbs. On

Abdominal examination, nontender firm hepatomegaly and ascites was present. No other organomegaly found and all other systemic examinations revealed no significant abnormality.

Regarding laboratory investigations, CBC showed thrombocytosis (platelet 690,000 cu/mm), hypoalbuminemia and hyperglobulinaemia, raised alkaline phosphatase level, HbA_1C- 7.9%. Ultrasound of the abdomen showed hepatomegaly, ascites, mild bilateral pleural effusion. Thyroid function test, renal function test, bilirubin, other liver function test, electrolytes, serum vitamin B_{12} level, tuberculin test, ANA, Viral markers were found within normal limit. Nerve conduction study of all four limbs showed severe sensory-motor demyelinating and axonal polyneuropathy of both upper and lower limbs (LL >UL) without any conduction block. The biopsy of the left cervical lymphnode showed reactive hyperplasia. Serum protein immunotyping showed IgG lambda monoclonal gammopathy, VEGF level raised (477 pg/ml; reference range, 31–86 pg/ml). Bone marrow aspiration cytology-normocellular marrow with plasmocytosis(plasma cell < 5%) and trilineage hematopoiesis, Bone marrow trephine biopsy- mild increase in a clonal plasma cell. X-ray pelvis shows some osteosclerotic lesions. Whole-body PET-CT revealed multiple enlarge metabolically active cervical, supraclavicular, axillary lymphnode and destructive lesion in dorsal, lumbar, left ischium, left lamina of C_2 vertebrae.

Pharmacologically he was treated lenalidomide and dexamethasone as 28 days cycle (lenalidomide 10mg day 1-21 and dexamethasone 40mg per day for 4 days in every wk for the first cycle). His tingling and numbness were improved, edema subsided but no significant improvement of motor function

Discussion:

Neurologists are frequently at the forefront of diagnosing POEMS syndrome. Diagnosis of POEMS is often delayed due to its rarity, lack of all the typical features and physicians' unfamiliarity with the entity.

POEMS syndrome differs from other para-proteinaemic and inflammatory neuropathies by its multi-organ involvement thought to be caused by elevated pro-inflammatory and angiogenic cytokines. As already stated, multi-organ features extend beyond those included in its acronym, and not all features included in the acronym are required for diagnosis[2-6,21].

Polyneuropathy is an initial presentation and essential feature of POEMS syndrome[2-4]. Initial presentation of our patient also consistent with features of polyneuropathy. Patients typically present with a subacute, distal, symmetrical, sensorimotor neuropathy, frequently painful, with allodynia and hyperpathia[3,22]. The lower limbs are affected earlier, and more severely than the upper limbs[3,23,24]. Sensory symptoms usually precede motor symptoms[23]. s. Many patients quickly become wheelchair- or bed-bound due to weakness or pain. The clinical examination may reveal distal wasting, weakness and sensory loss affecting both large and small fibre sensory modalities[3]. All these features were similar to our patient except sensory symptoms were started simultaneously with motor symptoms.

Electrodiagnostic studies demonstrate a length-dependent sensorimotor neuropathy, typically demyelinating, but with axonal degeneration. Conduction block is tended not usually present. In motor studies, reduction in motor conduction velocity (MCV) is an early sign, however, patients often already have a significant axonal loss at presentation[22-24]. Sensory studies show a reduction of, or often absent, sensory nerve action potentials [3,22-24]. Conduction block is much more common in CIDP than POEMS syndrome and the discrepancy in severity between upper and lowers limb axonal loss is more pronounced in POEMS syndrome [3,25]. Findings were similar to our patient showing absent SNAP in sural nerve and reduction of SNAP in the median and ulnar nerve . Prolonged latency and amplitude in median and ulnar nerve, no CMAP in the lower limb. No conduction block.

The constellation of neuropathy and any of the following should elicit an in-depth search for POEMS syndrome: monoclonal protein (especially lambda light chain), thrombocytosis, anasarca, or papilledema. Any patient who carries a diagnosis

of chronic inflammatory demyelinating polyneuropathy (CIDP) that is not responding to standard CIDP therapy should be considered as possibly having POEMS syndrome, and additional testing should be done to rule in or rule out the diagnosis of POEMS syndrome[19,20]. At the beginning of presentation, CIDP is also our concern but we examine and investigate to reach an appropriate diagnosis. The M protein is usually immunoglobulin (Ig) G or IgA and almost always of the lambda type[11-13.] Laboratory findings are notable for the absence of cytopenias. Nearly half of the patients have thrombocytosis or erythrocytosis[11-13]. Bone marrow usually contains less than 5% plasma cells, and, when clonal cells are found, they are almost always monoclonal lambda. Little is known about the plasma cells in POEMS syndrome except that more than 95% of the time they are lambda light chain restricted with restricted immunoglobulin light chain [15,26]. The bone marrow biopsy reveals megakaryocyte hyperplasia and megakaryocyte clustering in 54% and 93% of cases, respectively [11]. We have similar findings in our patient, IgG lambda monoclonal gammopathy, plasma cell 5%, thrombocytosis, increased megakaryopoiesis.

Osteosclerotic lesions occur in approximately 95% of patients and can be confused with benign bone islands, aneurysmal bone cysts, nonossifying fibromas, and fibrous dysplasia[19, 27]. Some lesions are densely sclerotic, whereas others are lytic with a sclerotic rim, whereas still others have a mixed soap-bubble appearance. FDG uptake occurs in those lesions that have a lytic component[28]. Lesions are commonly found in the pelvis, thoracic and lumbar vertebrae, and ribs, and also occur in the scapula, clavicle, sternum, skull and long bones normal. In our patient X-ray pelvis shows some osteosclerotic lesion and PET -CT of whole body revealed expansile/permeative bony destruction of thoracic, lumbar vertebrae, left ischium. In a retrospective cohort of 29 patients diagnosed with POEMS syndrome in India between 1983 and 2009, all had organomegaly, including hepatomegaly (28/29), splenomegaly (21/29) and lymphadenopathy (7/29). In our case, we found both hepatomegaly and lymphadenopathy but no splenomegaly found.

In a retrospective study of 64 patients with POEMS syndrome, 84% had endocrinopathy, 54% of whom had multiple endocrinopathies. Hypogonadism was commonest, affecting 79% of men. Other endocrine abnormalities described include thyroid dysfunction, abnormal calcium metabolism, glucose intolerance, diabetes, hyperprolactinemia, gynecomastia, and less commonly adrenal insufficiency[29,30]. In our case, we found diabetes mellitus, gynecomastia but thyroid function was normal and other hormonal evaluation was not done.

Skin changes are reported in as many as 90–100% of patients[7,10]. Hyperpigmentation and haemangiomas, thickening, hypertrichosis, acquired facial lipoatrophy, and infiltrated livedo reticularis with necrosis, acrocyanosis, flushing, rubor, hyperemia, and Raynaud's phenomenon may be the presentation. In our patient, we found multiple hyperpigmented lesions in different parts of body.

Helpful cut-offs for plasma and serum VEGF levels to diagnosis POEMS syndrome are 200 pg/mL (specificity 95%; sensitivity 68%)[9] and 1920 pg/mL (specificity 98%; sensitivity 73%),[9] respectively. The best cut-off of N-terminal propeptide of type I collagen to diagnosis POEMS syndrome 70 ng/mL with a specificity of 91.5% and a sensitivity of 80%[20]. In our patient VEGF level was raised (477 pg/ml; reference range, 31–86 pg/ml).

Evidence for treatment in POEMS syndrome is largely limited to retrospective cohort studies, with only one randomized controlled trial (RCT) to date. IVIg or steroid monotherapy, commonly used in other inflammatory neuropathies, does not produce a lasting benefit. The current suggested treatment algorithm recommends localized radiotherapy for patients with localized disease, defined as up to 3 discrete bone lesions and no evidence of clonal plasma cells on iliac crest biopsy, or systemic treatment in patients with diffuse disease, defined as >3 bone lesions or clonal plasma cells on iliac crest biopsy [31]. Systemic treatment options include ASCT or chemotherapy. Supportive treatment for neurological disability and systemic symptoms

should also be considered [31,32]. Lenalidomide is structurally similar to thalidomide but less neurotoxic. Two recent prospective studies, some small retrospective studies and a pooled analysis study have all shown it to be effective in POEMS syndrome, as either first- or second-line therapy [31,32] . Our patient having clonal plasma cell and multiple bony lesions with start lenalidomide and dexamethasone cyclical therapy .

Conclusion:

Though POEMS syndrome is a very rare, but treatable cause of neuropathy. Further work is required to establish its exact underlying pathophysiology. Current treatment approaches afford a good prognosis. Moving forward, randomized-controlled studies, though difficult given the rarity of POEMS syndrome, and the development of prognostic tools will be important in establishing individualized approaches to patient care. Most importantly if any suspected CIDP patient not improving with usual treatment, we should must exclude POEMS syndrome.

Conflict of interests: The authors declare that they have no conflict of interest

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