VOL. 35 NO. 2 ISSN 1023-4853 July 2019

BANGLADESH JOURNAL OF NEUROSCIENCE

CONTENTS

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Bangladesh Journal of Neuroscience

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

Clinical, Autonomic & Electrophysiological Features in Patients with Guillain Barre Syndrome in a Tertiary Care Hospital of Bangladesh

JANNAT M[1*], HANNAN MA[2], ALAM SM[3], ISLAM MR[4], CHOWDHURY AR[5], RAHMAN MH[6], DAS S[7], PATWARY SH[8], ISLAM MF[9], MASUM ASMHA[10]

Abstract:

Background: *Guillain-Barre Syndrome (GBS) is the most common cause of acute flaccid paralysis in the adult population. It is an acute post infectious immune mediated peripheral neuropathy with a marked variation in pathology, clinical presentation and prognosis.*

Objective: *The aim of the study were to evaluate clinical profile, to assess autonomic involvement & electrophysiological findings in adult patients with GBS.*

Methods: *An observational, cross sectional study was carried out in the Department of Neurology, BSMMU, Dhaka from March, 2015 to September, 2017. Total 43 patients of GBS fulfilling the inclusion criteria were recruited as the study population. Detailed clinical examination, CSF study & nerve conduction study were done. Disability status was measured by Hughes functional grading scale. For autonomic assessment 35 adult healthy control were also included for comparison. Then following tests of autonomic nervous system were performed in both patient and control group 1) resting heart rate and heart rate on changing posture (30: 15 ratio) 2) supine blood pressure and blood pressure on changing posture 3) heart rate response to valsalva maneuver 4) heart rate response to deep breathing and E: I ratio 5) sphincter disturbance by symptoms questionnaire.*

Results*: The mean age of patients was 35±12 years (range18 to 65 years) with slight male predominance (58.1%). Major clinical presentation was weakness of all 4 limbs followed by sensory complaints (44.2%). 7% of the patient had breathing difficulty and dysphagia. Only 4.7 % had diplopia. Among the symptoms of autonomic dysfunction most common symptoms was constipation (30.2 %) followed by palpitation (14%), urinary retention (7%), lightheadedness and urinary incontinence (4.7%). Cranial nerve palsy was present in 34.9% of cases among them facial palsy was found commonly (27.9%), followed by bulbar palsy (7%) and ophthalmoplegia (4.7%). One patient (2.3%) had both facial palsy and ophthalmoplegia. AIDP, AMAN and AMSAN subtypes comprised 32.6%, 37.2% and 20.9% of cases respectively. Regarding autonomic dysfunction variation of heart rate by different maneuver like posture change, deep breathing and valsalva maneuver was found commonly. 30:15 ratio was abnormal in majority of the*

1. Dr. Maftahul Jannat, Medical Officer, Department of Physiology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
2. Professor Dr. M. A. Hannan, Professor, Department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
3. Dr. Sheikh Mahbub Alam, Associate Professor, Department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
4. Professor Dr. Md. Rafiqul Islam, Professor & Chairman, Department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
5. Dr. Amit Roy Chowdhury, Specialist (Ex), Neurology Department, Square Hospital Limited.
6. Dr. Md. Habibur Rahman, Medical Officer, Upojela Health complex, Kishoregang.
7. Dr. Saumitra Das, Biochemist, Department of Biochemistry, Cumilla Medical College, Cumilla
8. Dr. A. M. Shafayet Hossain Patwary, Lecturer, Department of Anatomy, Noakhali Medical College, Noakhali
9. Dr. Md. Fakrul Islam, Assistant Professor, Department of Neurology, Dhaka Medical College, Dhaka.
10. Dr. Abu Shams Md. Hasan Ali Masum, Assistant Professor, Department of Neurology, Anowar Khan Modern Medical College, Dhaka.

patients (82.4%) followed by abnormal max-min HR/min on deep breathing (58.1%) and abnormal valsalva ratio (37.2%). Other abnormalities were postural hypotension (38.2%), sinus tachycardia (25.6%), hypertension (16.3%), hypotension (4.7%), and sinus arrhythmia (4.7%). Bowel bladder dysfunction was another autonomic dysfunction among them constipation 30%, urinary retention 7% and urinary incontinence 4.7% of cases.

***Conclusion:** GBS can be presented with variable presentation including autonomic dysfunction. In this study common clinical presentation was limb weakness & different patterns of autonomic dysfunction was found in patients with GBS. Common electrophysiological subtype was AMAN. So in addition to clinical & electrophysiological analysis autonomic evaluation is essential in every patients with GBS as autonomic dysfunction is one of important cause of mortality.*

***Key words:** Guillain Barre Syndrome (GBS), autonomic dysfunction, AIDP, AMAN, AMSAN, Hughes functional grading.*

Introduction:

Guillain-Barre syndrome (GBS) is an acute onset, immune-mediated disorder of the peripheral nervous system. The classic forms of GBS affects persons of all ages, but men are about 1.5 times more likely to be affected than women[1]. The mean annual incidence is1.1 to 1.8 per 100000 population[2].

A mild respiratory or gastrointestinal infection or immunization precedes the neuropathic symptoms by 1 to 3 weeks in approximately 60% of the patients[3]. The most common antecedent infection recognized before the onset of GBS is Campylobacter jejuni enteritis[4].

GBS is clinically characterized by acute flaccid paralysis, areflexia, mild sensory disturbance and albumino- cytological dissociation in the CSF. Rapidly progressive weakness is the core clinical feature of GBS. Maximum weakness is reached within 4 weeks, but most patients have already reached their maximum weakness within 2 weeks[5]. Besides motor and sensory deficits, GBS is often associated with a variety of autonomic involvement including cardiovascular, vasomotor, or sudomotor dysfunctions in both the sympathetic and parasympathetic systems.

Autonomic dysfunction of various degree has been reported in 65% of patients admitted to the hospital[6]. Most of the clinically significant autonomic dysfunction occurs with in the first 2-4 weeks of the illness, the peak period of paralysis. It's varied and complex manifestations may be related to either increased or decreased sympathetic – parasympathetic activity resulting in orthostatic hypotension, episodic or sustained hypertension, sinus tachycardia, tachyarrhythmia etc. Potentially serious bradyarrhythmias ranging from bradycardia to asystole were found in 7 to 34 % of patients[7]. Excessive vagal activity accounts for sudden episodes of bradycardia, heart block and asystole. Serious cardiac arrhythmia with haemodynamic instability tend to be more frequent in patients with severe quadriparesis and respiratory failure. Cardiovascular disturbances were found to be a common feature of patients with GBS who were severely paralyzed, requiring assisted ventilation[8]. Severe autonomic dysfunction is an indication for ICU admission[9]. Acute autonomic dysfunction develops in the majority of patients with GBS and is a significant cause of death in these patients[10].

Electrophysiologically GBS is categorized into demyelinating (acute inflammatory demyelinating polyneuropathy-AIDP) and axonal (Acute motor axonal neuropathy-AMAN and Acute motor sensory axonal neuropathy-AMSAN) varieties[1]. These varieties are difficult to distinguish on clinical grounds alone and electrophysiology plays a determinant role in GBS diagnosis, classification of the subtypes and in establishing the prognosis[11].The frequency of AIDP and AMAN in the whole GBS population varies substantially between the countries. AMAN variety of GBS is more prevalent in the northern China, central and South East Asia and South America; whereas AIDP is more frequent in the Europe and North America[12]. Axonal variant of GBS is more frequent

in Bangladesh, associated with preceding Campylobacter jejuni infection[13].

Methods:

This Cross sectional observational study was conducted in the department of Neurology BSMMU, Dhaka from March, 2015 to September, 2017. Total 43 patients of GBS fulfilling the inclusion criteria were recruited as the study population. Detailed clinical examination, CSF study & nerve conduction study were done. Disability status at the time of autonomic testing was measured by Hughes functional grading scale. For autonomic assessment 35 adult healthy control were also included for comparison. Then following tests of autonomic nervous system were performed in both patient and control group 1) resting heart rate and heart rate on changing posture (30: 15 ratio) 2) supine blood pressure and blood pressure on changing posture 3) heart rate response to valsalva maneuver 4) heart rate response to deep breathing and E: I ratio 5) sphincter disturbance by symptoms questionnaire.

Statistical analysis

The medical records demographic, clinical, laboratory, NCS report and autonomic profile of the patients and control were recorded in the preformed data sheet. At the end of data collection, all the data were rechecked, coded and entered in standard statistical software used in BSMMU, data base using SPSS software (Version-24). Demographic variables were analyzed by Chi square test. Qualitative data were expressed as frequency and percentage. Quantitative data were expressed as mean ±SD.

Results and observations:

In this study the mean age (±SD) was 35 (±12) years (Table I). Higher frequency of GBS was found in male (58.1%) than female (Table 2). Most common presentation was weakness of all four limbs (100%) with lower limb weakness more than upper limb weakness. Sensory complaints were present in 44.2% of patients (Table 3). Common cranial nerve palsy was lower motor type facial palsy (27.9%). Bulbar palsy was present in 7% and ophthalmoplegia in 4.7% of cases. Among them one patient (2.3%) had both facial palsy and ophthalmoplegia. Symptoms of autonomic dysfunction was present in 39.5 % of cases among them constipation 30.2%, palpitation 14%, lightheadedness & dizziness 4.7%, urinary retention 7% and urinary incontinence 4.7% of cases (Table 4). Total cranial nerve palsy was present in 34.9% of cases. Disability status of majority of the patient (35%) was grade 4 severity according to Hughes functional grading scale. Nerve conduction studies showed majority of the patients (37.2%) having acute motor axonal neuropathy (AMAN) variety followed by acute demyelinating polyradiculoneuropathy (AIDP) & acute motor sensory polyradiculoneuropathy (AMSAN) in 32.6 & 20.9% of cases respectively. About 9.3% of cases could not be categorized into specific groups (Figure: 1). 27.9% of patients were treated with plasma exchange during their course of illness and 2.3 % of patient received intravenous immunoglobulin. Majority of the patients (69.8%) received no definite treatment (Table: 5). Among autonomic dysfunction variation of heart rate on different maneuver like changing posture (30:15 ratio 82.4%), deep breathing (58.1%) and valsalva maneuver (37.2%) were found commonly. Other autonomic dysfunction were postural hypotension 38.2 %, Sinus tachycardia 25.6%, hypertension 16.3%, hypotension and sinus arrhythmia 4.7% of cases (Table 6).

Table-I

Distribution of study population by age groups (n=43)

Age range	Number	Percentage
18 to 25 Yrs	13	30.2%
26 to 35 Yrs	12	27.9%
36 to 45 Yrs	11	25.6%
46 to 55 Yrs	4	9.3%
56 to 65 Yrs	3	7%
Total	43	100%
Mean (±SD)	35 (±12)	

Table-II

Gender distribution of patients (n=43)

Gender	Patient (n=43)	Percentage
Male	25	58.1%
Female	18	41.9%
Total	43	100%

Table-III

Presenting complaints of the patients (n=43)

	Frequency	Percentage
Weakness- lower limbs>upper limbs	43	100
Sensory complaints	19	44.2
Breathing difficulty	3	7
Dysphagia	3	7
Diplopia	2	4.7

Table-IV

Symptoms of autonomic dysfunction

Symptoms	Frequency (n=43)	Percentage
Constipation	13	30.2
Palpitation	6	14
Lightheadedness/ dizziness	2	4.7
Urinary retention	3	7
Urinary incontinence	2	4.7
Total		39.5

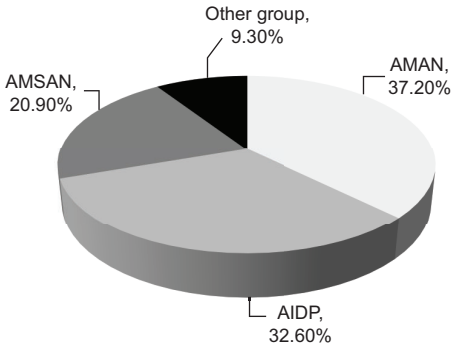

Fig.-1: *Distribution of patients according to electrophysiological features (n=43)*

Table-V

Patients receiving definite treatment (n=43)

Treatment modality	N (%)
Plasma Exchange	12 (27.9%)
I/V Immunoglobulin	1 (2.3%)
No definite treatment	30 (69.8%)
Total	43 (100%)

Table-VI

Frequency and pattern of autonomic dysfunction among patients with GBS (n=43)

Autonomic dysfunction	Frequency	Percentage
Tachycardia	11	(25.6)
Sinus Arrhythmia	2	(4.7)
Hypertension	7	(16.3)
Hypotension	2	(4.7)
Postural Hypotension	13	(38.2)
Abnormal 30:15 ratio	28	(82.4)
Abnormal Max-Min HR on deep breathing	25	(58.1)
Abnormal Valsalva ratio	16	(37.2)
Constipation	13	(30)
Urinary retention	3	(7)
Urinary incontinence	2	(4.7)

Discussion:

In this study, the mean age was found 35(±12) years & majority of the study patients were young adults of 18-35 years (58.9%). Mean age of GBS patients in another study done by[14] was found 34.75(±16.59) years. In our study incidence of GBS was slightly prevalent in male (58.1%) than female (41.9%), it has similarities with the one previous study[15]. History of preceding infection was found in 76.8 % of patients which coincides with the different study done in Bangladesh[16,13].

In this study all patients were presented with varying degree of weakness of all four limbs and other common symptoms were sensory complaints (44.2%), symptoms of autonomic dysfunction like lightheadedness on changing posture, palpitation, constipation, urinary retention and incontinence were present in 39.5% of the patients & cranial nerve palsy was found in 34.9% of cases.

The present study found predominant subtype AMAN (37.2%) followed by AIDP (32.6%) and AMSAN (20.9%). Around 9.3% (4) of the patients in our study constitute other group as they could not be categorized by any of the above subgroup. Three of them had normal NCS findings and one of them had regional variant. So axonal variants (AMAN and AMSAN) constitute the predominant subtype (58.1%) in our population. A study done in Bangladesh, also found higher frequency of axonal variants in 67% (AMAN 56% and AMSAN 11%) followed by AIDP in 22% of cases[13].

Incidence of autonomic dysfunction in GBS has been reported to vary considerably. Autonomic dysfunction in GBS probably occurs even more frequently than recorded as some of its manifestations are quite transient and require continuous monitoring. Sustained sinus tachycardia is the most commonly observed manifestation found in 37% of cases as described by different authors[18,19]. Sinus tachycardia was present in 25.6% of cases in our study. Sinus arrhythmia was found in only two of our patients. In this study hypertension was found in 16.3% and hypotension in 4.7% of cases.

Postural hypotension is another important and common manifestation in GBS. We had found 38.2% of patients with postural hypotension that coincides the other study[19]. The percentage of postural hypotension may be even higher as it could not evaluated in few patients in our study due to severe weakness.

Regarding bowel and bladder dysfunction we found 30% of patients had constipation but it was found in 15% of cases in another study [18]. Only 3 (7%) of the patient had urinary retention during the course of the illness and two of them had urinary incontinence.

As we observed only 31.2% (13) of the patients received definitive treatment among them 12 patients received plasma exchange and 1 patient was treated with intravenous immunoglobulin. Most of the patients were unable to receive these costly treatment due to financial constrain. The current study was done to detect autonomic dysfunction in addition to clinical features and treat accordingly thus helps those patients to reduce sufferings.

Conclusion:

GBS can be presented with variable presentation including autonomic dysfunction. In this study common clinical presentation was limb weakness & different patterns of autonomic dysfunction was found in patients with GBS. Common electrophysiological subtype was AMAN. So in addition to clinical & electrophysiological analysis autonomic evaluation is essential in every patients with GBS as autonomic dysfunction is one of important cause of mortality.

Ethical issues:

All patients gave informed written consents and the study was approved by Institutional Review Board of Bangabandhu Sheikh Mujib Medical University.

Conflict of interests:

The authors declare that they have no conflict of interest.

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Demographic and Clinical Pattern of Headache in Migraine Patients

MAJUMDER B[1], PAUL D[2], BARMAN KK[3], FERDOUSHI S[4], ISLAM MR[5], ROY NR[6], SALEHEEN MS [7], ISLAM MM[8]

Abstract

Background: *Migraine is one of the most common neurological disorder and fourth most important factor for debility in human. The presentation of migraine is complex. All patients do not have same features of migraine.* ***Objectives:*** *The purpose of the study was to evaluate demographic and clinical patterns of headache in migraine patients.* ***Methods:*** *A total of 30 migraine patients who were visited in the Headache clinic, Department of Neurology, BSMMU, Dhaka were enrolled for the study. Migraine patients diagnosed according to ICHD-3 (International Classification of Headache Disorders 3rd edition) criteria.* ***Results:*** *Out of 30 patients mean age was 30.63±10.95 years with age range 15-60 years in migraine patients. Female were more common. Positive family history was present in 56.7% patients. Common associated symptoms were photophobia, phonophobia (96.7%) and nausea (83.3%) in migraine patients. Common precipitating factors were stress and sunlight (90%) followed by journey (80%) and insomnia (73.3%). A major portion of migraine was without aura (73.3%) and the ratio of aura to without aura is 1: 2.75. Major portion of migraine patients were complained of 4-6 attacks/ month (46.7%) which was followed by 1-3 attacks/month (36.7%). Most of the migraine patients complained as moderate headache (60%) followed by severe headache (40%).* ***Conclusion:*** *This study concluded that migraine is a disease of younger age group and it affects female more commonly than male, pattern of headache in migraine patients is unique.*

Introduction:

Migraine is the primary headache disorder and the second most common neurological (next to nutritional disorders and neuropathies) problem throughout the world[1]. Annually it affects 12% population of the United States. It includes 18% women, 6% men and 4% children in the United States. Overall, the 1-year prevalence of migraine ranged from 3.0% in aged 11-14 years and 10.6% in age ranging from 5-15 years[2]. All the subtypes of migraine were more common in females[3] which is also consistent with the study done in Bangladeshi populations[4].

Migraine is a familial disorder characterized by recurrent attack of headaches widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting[5]. In some cases, they are preceded by or associated with neurological and mood disturbances. Migraine sufferers typically have unilateral headache but it may be bilateral and complain of throbbing headache but equally it may be constant. They usually have some degree of nausea and/ or vomiting and often have sensitivity to light (photophobia) or sensitivity to sound

1. Dr. Bipasha Majumder, Medical Officer, Dept. of Laboratory Medicine , DMCH, Dhaka.
2. Dr. Debatosh Paul, Associate Professor, Dept. of Laboratory Medicine, BSMMU, Dhaka.
3. Dr. Kanuj Kumar Barman, Associate Professor, Dept. of Neurology, BSMMU, Dhaka.
4. Dr. Sheuly Ferdoushi, Associate Professor, Dept. of Laboratory Medicine, BSMMU, Dhaka.
5. Prof. (Dr.) Md. Rafiqul Islam, Professor and Chairman, Dept. of Neurology, BSMMU, Dhaka.
6. Dr. Niloy Ranjan Roy, IMO, Dept. of Neurology, DMCH, Dhaka.
7. Dr. Md. Shafiqus Salehin, Assistant Professor, Dept. of Neurology, M Abdur Rahim Medical College, Dinajpur
8. Dr. Md. Monirul Islam, Registrar (Medicine), Satkhira Medical College, Satkhira

(phonophobia)[6]. Normal physical activity that involves movement of the head aggravates the pain. Human biology knows few rules that do not have exceptions and many patients did not have all the features of migraine[7].

The presentation of migraine is complex. Two common clinical syndromes associated with migrainous headache can be identified easily that is migraine with aura and migraine without aura. Migraine with aura is called classical or neurologic migraine and migraine without aura is known as common migraine. The ratio of classical to common migraine is 1:5[8].

Some precipitating factors for headache are fatigue, stress, anxiety, cold, warm, sunlight, sleep deprivation/insomnia, food, activity, journey, reading etc. There are 5 relieving factors of headache such as sleep, drug, rest, posture, massage[9].

Aims and objectives:

To evaluate the demographic and clinical pattern of headache in migraine patients.

Materials and Methods:

This cross sectional analytical study from March, 2018 to February, 2019 was conducted in the Department of Laboratory Medicine, BSMMU, Dhaka, collaboration with the Department of Neurology, BSMMU, Dhaka. After ethical clearance from Institutional Review Board (IRB), patients having features of migraine according to ICHD-3 (International Classification of Headache Disorders, 3rd edition) was selected as study population by purposive sampling method.

Total 30 headache patients selected from headache clinic of outpatient department of Neurology of BSMMU. Age range of study group was 10-60 years. Informed written consent was taken from each patient.

Results:

The study included 30 migraine headache patients. Table I shows age group of study population, where the maximum number of patient 12(40.0%) in 21-30 age group. The mean age was 30.63±10.95.

Table-I

Age distribution of study subjects (n=30)

Age of the patient	Migraine headache patient (n=30) No. (%)
<20	5(16.7)
21-30	12(40.0)
31-40	9(30.0)
41-50	3(10.0)
51-60	1(3.3)
Total	30(100.0)
Mean ±SD	30.63±10.95

Table-II

Gender distribution of study subjects (n=30)

Gender	Migraine headache patient (n=30) No. (%)
Male	3(10.0)
Female	27(90.0)
Male: Female ratio	1:9

Table II shows the gender distribution of patients. Among 30 respondents 10% were male and 90.0% were female.

Table-III

Distribution of the study subjects by occupation (n=60)

Occupation	Migraine headache patient (n=30) No. (%)
Service holder	3(10)
Business	0(0)
Housewife	15(50)
Others	12(40)
Total	30 (100)

Table-III shows maximum 50.0% patients were housewife, 10% patients were service holder and 40.0% patients had other profession.

Figure-1: Bar diagram showing the family history of migraine headache patient (n=30)

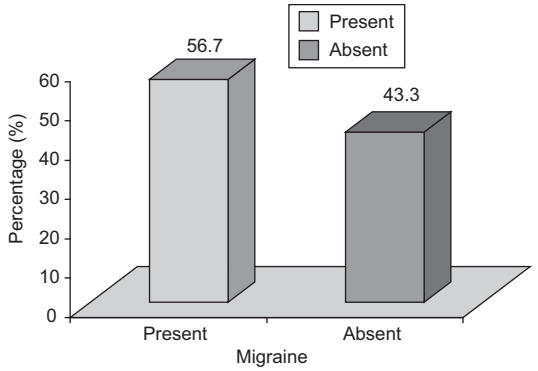

Fig.-1: *Bar diagram shows maximum patients 56.7% had positive family history and 43.30% having no family history of migraine.*

Figure-2: Bar diagram showing the severity of the headache in migraine patients (n=30).

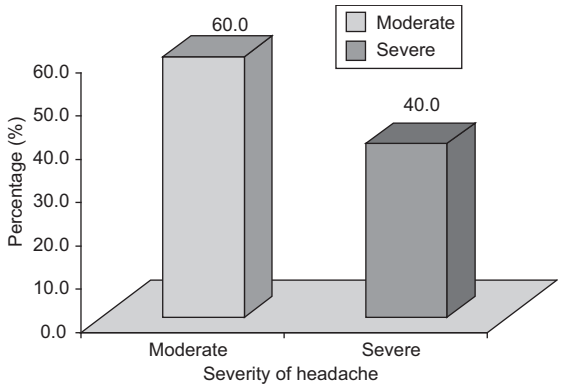

Fig.-2: *Bar diagram shows maximum patients 60% had moderate headache and 40.0% severe headache.*

Figure 3: Pie chart shows that a major portion of migraine patients were without aura (73.3%). Only 26.7% migraine patients gave history of experiencing aura.

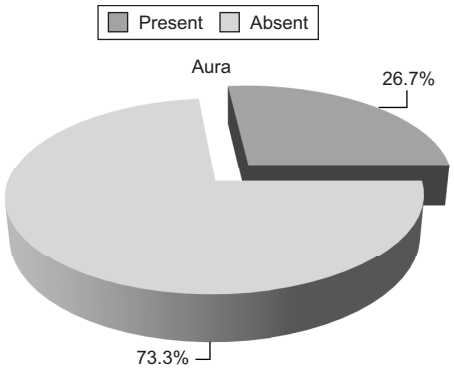

Fig.-3: *Pie chart showing distribution of migraine headache patient according to aura (n=30)*

Table-IV

Distribution of the migraine headache patient by frequency of attacks per month (n=30)

Frequency of attacks per month	No. of the Patient	Percentage
1-3	11	36.7
4-6	14	46.7
7-9	3	10.0
10-12	1	3.3
13-15	1	3.3
Total	30	100.0

Table-IV shows frequency of attacks of headache per month maximum 46.7% in 4-6 times, 36.7% patients had 1-3 times, 10.0% patients had 7-9 times and 3.3% patients had 10-12 times and 13-15 times.

Table-V

Distribution of the migraine headache patient with associated symptoms (n=30)

Associated symptom	Frequency	Percentage
Nausea	25	83.3
Vomiting	12	40.0
Vertigo	21	70.0
Phonophobia	29	96.7
Photophobia	29	96.7
Difficulty in concentrating/ Feeling lightheadedness	28	93.3

Table- V shows that the most common announcing associated symptoms were nausea (83.3%), phonophobia and photophobia (96.7%) in migraineurs.

Table-VI

Distribution of the migraine headache patient with precipitating factors (n=30)

Precipitating factors	Frequency	Percentage
Stress	27	90.0
Journey	24	80.0
Sunlight	27	90.0
Insomnia	22	73.3
Deprivation of food	5	16.7
Menstruation	2	6.7
OCP	8	26.7

Table-VI shows that a major portion of migraine patients proclaimed stress (90%), sunlight exposure (90%) as precipitating factors for migraine which was followed by journey (80%) and insomnia (73.3%).

Table-VII

Distribution of the migraine headache patient with relieving factors (n=30)

Relieving factors	Frequency	Percentage
Rest	27	90.0
Sleep	28	93.0
Massage	22	73.0
Others (Hot & cold compression)	03	10

Table –VII shows that reported relieving factors of migraine patients are rest (90%), sleep (93%) and massage (73%).

Discussion:

This cross sectional study was carried out to see the demographic variations among the migraine headache patient. In this study, it was observed that maximum number of patient 12(40.0%) in the age group 21-30. The mean age was 30.63±10.95. Mean age 39.6 ± 11.1 and 37.7 ± 11.1 years respectively were also found[10]. Some study shows that migraine may start in early childhood. But its prevalence increases at 10 to 14 years of age and continues to increase until 35 to 39 years of age. Then it gradually decreases, particularly women after menopause[11]. These results are nearly similar to our study.

Among 30 respondents 10% male and 90.0% females were migraine headache patients. Female respondents were predominant. Female groups were more prone to develop migraine 69.3% and 81.7% respectively[12,13].

A major portion of migraine patients were housewife (50%) which was followed by student or other (40%). Housewife were the large group (28.6%) followed by student (17.6%) found in another study[14]. These are almost similar with our study. The possible reason may be in our country the housewives are more exposure to many provocative factors like physical and mental stress, irregular of food, menstruation, birth control pill intake etc.

Migraine has a strong genetic component and the familial risk of migraine is increased as exhibited by population-based family studies[15] which coincides with our study where 56.7% of migraine patients had family history of migraine headache.

Migraine headache severity was divided into mild, moderate and severe group according to visual analogue scale. Among the migraine patients, most of the patients complained of moderate headache which is about 60% followed by severe headache (40%). But no one complained headache severity as mild. According to International Classification of Headache Disorder migraine headache severity is moderate to severe intensity[16] which is also consistent with our study.

Among the 30 migraine patients, 08 (26.7%) patients had migraine with aura and 22 (73.3%) patients had migraine without aura and the ratio is 1:2.75. Another study[17] found that among 32 subjects, 26% (7) patients had migraine with aura and 74% (20) patients had migraine without aura, ratio was 1:2.85 which is almost similar to our study. In another study[8] found the ratio of migraine with aura to migraine without aura is 1:5 which is near to our study.

A major portion of migraine patients were complained of 4-6 attacks/month (46.7%) which was followed by 1-3 attacks/month (36.7%). Another study done in this country[14] reported as 30.76% patients suffer 3 or less attacks per month and 4 or more attacks in 16.15% per month.

According to associated symptoms of migraine, the most common announcing associated symptoms were photophobia (96.7%), phonophobia (96.7%) and nausea (83. 3%) in migraine patients. Another study[18] shows that most common symptoms associated with headaches were phonophobia (91.6%) and photophobia (85.4%).

Most of the migraine patients, proclaimed stress and sunlight as precipitating factors of migraine (90%) which was followed by journey (80%) and insomnia (73.3%). Another study[19] showed that most common precipitating factors were stress,

tension, not eating on time, fatigue and lack of sleep. Similar result was[20] mentioned that the most frequent triggers of migraine were mental exertion, exposure to the sunlight, heat and anxiety.

Most common relieving factor for migraine patients are sleep (93%) and rest (90%). Another study[14] reported analgesic (83%), sleep (80%) which is consistent with the present study.

Conclusion:

This study showed that migraine headache was common in young age group and female predominant. This study may also provide baseline information regarding migraine headache pattern.

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Bangladesh Journal of Neuroscience 2019; Vol. 35 (2): 69-77

Infarct Pattern in Patients with Varying Degrees of Internal Carotid Artery Stenosis

MUZAHID MAA[1*], SHAIKH MAK[2], SHAHIDULLAH M[3],CHOWDHURY A[4], SAHA S[5], ROY U[6], KABIR MS[7],DEY SK[8],AHMED A[9], ISLAM MR[10].

Abstract:

***Background**: Internal carotid artery (ICA) is one of the commonest site stenosis in patients with ischemic stroke. There is difference in the distribution of stenosis among different sites of cerebral infarct.Volume and severity of cerebral infarct may also depend on the degree of stenosis. To plan efficient evaluation and treatment of individual patient of ischemic stroke, the responsible clinician must be familiar with the relative probability of finding occlusive lesions at various sites within the vascular tree. **Objective:** The objective of this study was to evaluate the angiographic pattern of ICA stenosis among different types of cerebral infarct. **Materials and Methods**: We evaluated 53 ischemic stroke patients from indoor, outdoor, stroke and neuro intervention clinic, BSMMU. CT scan and/ or MRI of brain were done to each patient to confirm the diagnosis. After vascular imaging, the degree of stenosis was measured by the NASCET formula. **Results:** Cervical segment of ICA was most commonly [n=45(84.9%)] encountered site of stenosis and total occlusion of ICA was always observed in cervical segment. Among patients with moderate stenosis (n=15) of ICA, 6(40.0%) presented with subcortical infarction, 4(26.7%) presented with lacunar infarction and 5(33.0%) presented with territorial infarction. In case of severe stenosis (n=23), territorial, lacunar and watershed infarct were 9(39.1%), 8(34.8%) and 2(8.7%) respectively. Whereas total occlusion (n=15) of ICA presented as either territorial infarction [n=11(73.3%)] or watershed infarction [n= 4(26.7%)]. These differences between severity of stenosis and subtype of infarct were also significant (p-value = 0.003).A total of 25 patients presented with territorial infarction, mostly MCA territory [n=23(92%)]. **Conclusion:** With increasing severity of stenosis, the infarct burden rises. ICA stenosis of e"70% mainly presented as territorial infarction whereas, watershed infarct was an indicator of severe stenosis.*

***Key Words**: Ischemic Stroke, ICA Stenosis,Angiography,Infarct Pattern.*

Introduction:

There are over 13.7 million new strokes each year and one in every four people worldwide over the age of 25 will experience a stroke in their lifetime[1]. Worldwide, 70% of strokes and 87% of both stroke-related deaths and disability-adjusted life years occur in the developing areas. On average, stroke occurs 15 years earlier in these areas affecting individuals at the peak of their productive life[2]. According to the latest WHO data from 2020, stroke deaths in Bangladesh reached 118,918 or 15.31% of total deaths. The age adjusted death rate is 110.89 per 100,000 of population, which ranks Bangladesh 41 in the world[3].

Atherosclerosis affecting extracranial and intracranial blood vessels is an important and well recognized cause of cerebral ischemia. Carotid atherosclerosis is recognized as the most common vascular lesion in stroke patients[4]. Stroke risk is ten times higher in patients with more than 80%

1. Md. Abdullah Al Muzahid, Phase B Resident, Department of Neurology, BSMMU.
2. Md. Abdul Kader Shaikh, Associate Professor, Department of Neurology, BSMMU.
3. MD. Shahidullah, Associate Professor, Department of Neurology, BSMMU.
4. Ashish Chowdhury, Phase B Resident, Department of Neurology, BSMMU.
5. Sujan Saha, Phase B Resident, Department of Neurology, BSMMU.
6. Uttam Roy, Phase B Resident, Department of Neurology, BSMMU.
7. Md. Suman Kabir, Phase B Resident, Department of Neurology, BSMMU.
8. Subash Kanti Dey, Associate Professor, Department of Neurology, BSMMU.
9. Anis Ahmed, Assistant Professor, Department of Neurology, BSMMU.
10. Md. Rafiqul Islam, Professor and Chairman, Department of Neurology, BSMMU.

stenosis of carotid arteries than patients with less than 40% carotid stenosis[5]. Atherosclerosis of major cerebral arteries leads to changes ranging from minor wall thickening to near total occlusion, and may occur in isolation or with systemic atherosclerosis[6]. In situ thrombotic occlusion, artery-to-artery embolism, hypoperfusion, branch atheromatous disease or the combination of these mechanisms lead to cerebral ischemia in patients with atherosclerotic stenosis[7].

Embolism from proximal artery may cause acute obstruction of distal cerebral arteries producing territorial infarction or lacunar infarction, whereas hemodynamically significant stenosis or obstruction of intracranial arteries may cause ischemia in the distal regions of hemisphere causing the so-called border zone infarction[8]. Collateral flow through circle of Willis and collaterals from pial arterioles connecting two major cerebral arteries affect significantly the outcome of acute arterial obstruction by providing alternate routes for blood flow in the setting of acute ischemic stroke[4].

Methods

Patient selection

This cross-sectional observational study was carried out with an aim to find out the infarct pattern of ICA stenosis among different subtypes of ischemic stroke patients purposively selected from Inpatient, Outpatient and Stroke & Neuro-Intervention clinic of BSMMU. Only the patients with first ever ischemic stroke having significant symptomatic stenosis (≥50% stenosis) on angiography, presenting within 14 days of symptom onset were included in this study. Patients with previous stroke, concomitant arterial embolism of limbs or other parts of body, or presumed cardio-embolic sources (rheumatic heart disease, atrial fibrillation, prosthetic heart valves, recent myocardial infarction, cardiomyopathy) were excluded.

Clinical evaluation

Total 155 patients with ischemic stroke were preliminarily selected, among them 12 had previous stroke, 17 had cardioembolic factors present and were excluded. 25 patients had normal angiographic findings and 40 patients having stenosis in vessel other than ICA were excluded from the study. 8 patients had insufficient data and were excluded. So total 53 patients with ischemic stroke who had significant stenosis of ICA were selected as cases. After ethical clearance from Institutional Review Board (IRB), informed written consent was taken from each patient or his/her attendant. Proper history was taken, physical and neurological examination, keeping in mind of the demographic and clinical variables, were done. All relevant investigations were completed including CT Scan of brain or MRI of brain with DWI sequence.

Angiographic Evaluation

Cerebral angiogram was performed within 30 days of presentation. Angiography was performed by any of the modalities like MRA, CTA or DSA, the one being more feasible for the patient, as advised by the attending consultant. In total 48 of our patients underwent DSA and 33 patients underwent TOF MRA. In angiogram, the degree of stenosis was measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[9].

Percentage of Stenosis = $[(Dn - Ds)/Dn] \times 100$, where Dn is normal diameter and

Ds is stenosed diameter.

Then, we classified the patients into 3 groups according to the following grading scale: moderate (50%–69%), severe (70–99%), or total occlusion (no flow detected)[10]. A stenotic lesion which was at or above the petrous part of ICA was considered as intracranial stenosis whereas, stenotic lesion proximal to the petrous part of ICA was considered as extracranial stenosis[11].

Topography of infarct

Topography of infarct was determined by commonly accepted arterial territories and watershed areas[12]. Each infarct was subdivided into one of four subtypes: territorial, subcortical, lacunar or watershed zone infarct.Territorial infarction was considered when a large ischemic lesion involving the cerebral cortex and subcortical structures in 1 or more major cerebral artery territories was encountered[8]. It was subdivided into ACA, MCA or PCA territory infarct according to accepted cortical supply[12]. Subcortical infarction was considered when (a) the infarcts are restricted to the basal ganglia and/or white matter and the overlying cerebral cortex appears normal; and (b) the maximum diameter of the lesion was more than 20mm[13]. Small infarcts, occurring in the white matter, deep grey matter nuclei, and brainstem;

and of less than 15mm in diameter was considered as lacunar infarct[14]. Watershed infarction were lesions in one of the hemodynamic risk zones between major cerebrovascular territories: the superficial border zones wedged between the ACA and MCA or between the MCA and PCA, and the deep border zone located in the vascular territory between deep and superficial arterial systems[8].

Statistical Analysis

All the data were rechecked after collection. Continuous variables were expressed as Mean ± SD. Categorical variables were presented by frequency, percentage and graph. Qualitative data were analyzed by chi-square test. P value of < 0.05 was considered statistically significant. Statistical analysis was done using SPSS (Statistical Package for Social Sciences) windows version 26.0 software program.

Results and observations:

In this study, mean (±SD) age was 58.83±9.85 years with range from 35-77 years. 35 were male and 18 were female with male female ratio of 1.94:1 (Table I). Most frequently observed age group was 60-69 year having 22(41.5%) patients. In total 15 patients had moderate stenosis, 23 patients had severe stenosis and 15 patients had total occlusion of ICA (Figure 2). Cervical segment of ICA was most commonly [n=45(84.9%)] encountered site of stenosis and no stenosis was found in petrous segment (Figure 3). Total occlusion of ICA was always observed in cervical segment.Among 45

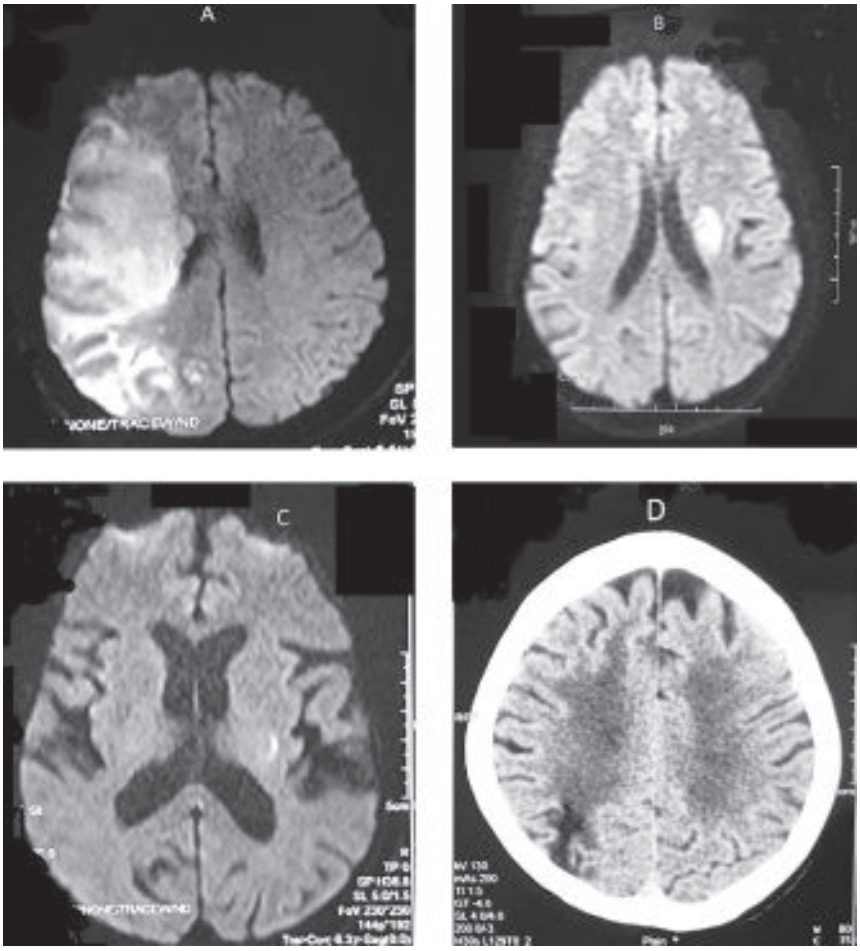


Fig.-I: *Definition of infarct pattern. A: MRI-DWI sequence showing territorial infarct involving right MCA territory. B: MRI-DWI sequence showing subcortical infarct involving left side. C: MRI-DWI sequence showing lacunar infarct involving left internal capsule. D: CT scan showing watershed infarct between right MCA and PCA territory.*

patients with stenosis of cervical segment of ICA, 24(53.3%)had territorial infarct, 8(17.8%)had lacunar infarct, 7(15.6%)had subcortical infarct and 6(13.3%)had watershed infarct. Four patients with stenosis in cavernous part had subcortical [n=2(50.0%)] and lacunar [n=2(50.0%)] infarct. Four patients with stenosis in supraclinoid part had lacunar [n=3(75.0%)] and territorial [n=1(25.5%)] infarct. This observation was statistically significant (p- value = 0.041) (Table II).

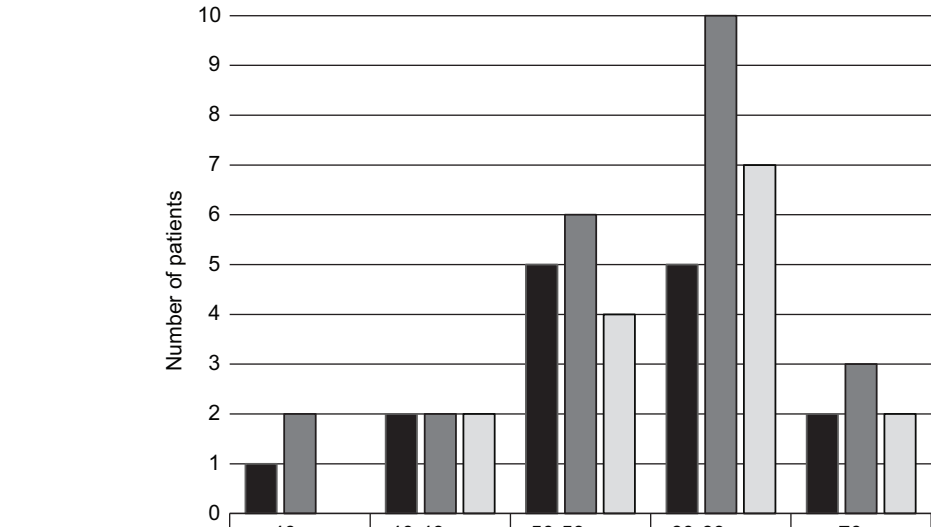
Among 15 patients with moderate stenosis of ICA, 6(40.0%) presented with subcortical infarction, 4(26.7%) presented with lacunar infarction and 5(33.0%) presented with territorial infarction. In case of severe stenosis, territorial, lacunar and watershed infarct were 9(39.1%), 8(34.8%) and 2(8.7%) respectively. Whereas total occlusion of ICA presented as either territorial infarction [n=11(73.3%)] or watershed infarction [n= 4(26.7%)]. These differences between severity of stenosis and subtype of infarct were also significant (p-value = 0.003) (Table III).A total of 25 patients presented with territorial infarction, mostly MCA territory[n=23(92%)]. ACA and PCA territory were observed in 1(4.0%) each (Table IV).

Table-I

Distribution of age of the study population according to sex type (n=53)

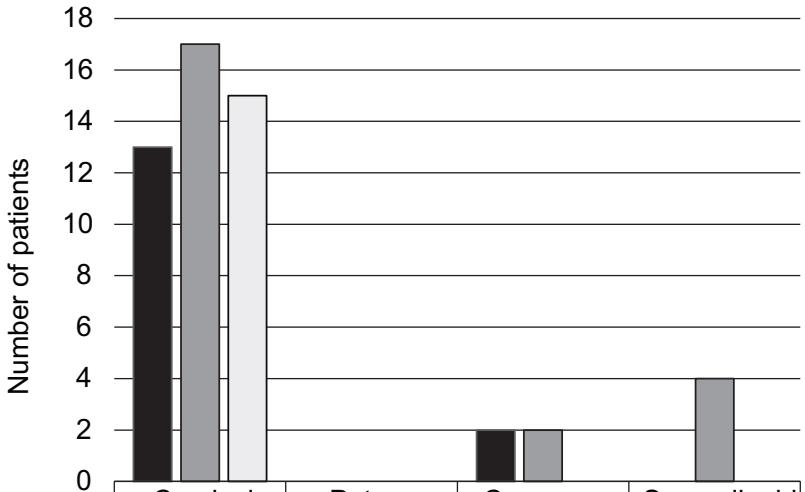
Age of Patient	Sex type of Patient		Total	P-value
	Male	Female		
<40 years	2(5.7%)	1(5.6%)	3(5.7%)	0.979^{ns}
40-49 years	4(11.4%)	2(11.1%)	6(11.3%)	
50-59 years	10(28.6%)	5(27.8%)	15(28.3%)	
60-69 years	15(48.9%)	7(38.9%)	22(41.5%)	
e”70 years	4(11.4%)	3(16.7%)	7(13.2%)	
Total	35(100.0%)	18(100.0%)	53(100.0%)	
Mean±SD	58.4±9.28	59.71±10.89	58.83±9.85	
Range(Min – Max) years	35-77			

ns: significant (P value > 0.05), figures in the parentheses indicate correspondingpercentage;
Chi-squared (c^2)Test was done to analyze the data.



	<40 yrs	40-49 yrs	50-59 yrs	60-69 yrs	≥ 70 yrs
Moderate stenosis	1	2	5	5	2
Severe stenosis	2	2	6	10	3
Total occlusion	0	2	4	7	2

Fig.-2: *Bar diagram showing distribution of age of the study population according to severity of stenosis (n=53).*



	Cervical	Petrous	Cavernous	Supraclinoid
Moderate stenosis	13	0	2	0
Severe stenosis	17	0	2	4
Total occlusion	15	0	0	0

Fig.-3: *Bar diagram showing distribution of different segments of ICA according to severity of stenosis (n=53).*

Table-II

Distribution of different segments of ICA according to subtype of infarct (n=53)

Segment of ICA	Subtype of Infarct				Total	p-value
	Territorial (n=25) No. (%)	Subcortical (n=9) No. (%)	Lacunar (n=13) No. (%)	Watershed (n=6) No. (%)	(n=53) No. (%)	
Cervical	24(53.3%)	7(15.6%)	8(17.8%)	6(13.3%)	45(100%)	0.041*
Cavernous	0(0.0%)	2(50.0%)	2(50.0%)	0(0.0%)	4(100%)	
Supraclinoid	1(25.0%)	0(0.0%)	3(75.0%)	0(0.0%)	4(100%)	
Total	25(47.2%)	9(17.0%)	13(24.5%)	6(11.3%)	53(100%)	

* significant (P value d" 0.05), figures in the parentheses indicate correspondingpercentage;
Chi-squared (c^2)Test was done to analyze the data.

Table-III

Distribution of severity of stenosis according to subtype of infarct (n=53)

Severity of Stenosis	Subtype of Infarct				Total	p-value
	Territorial (n=25) No. (%)	Subcortical (n=9) No. (%)	Lacunar (n=12) No. (%)	Watershed (n=6) No. (%)	(n=53) No. (%)	
Moderate	5(33.3%)	6(40.0%)	4(26.7%)	0(0.0%)	15(100%)	0.003*
Severe	9(39.1%)	4(17.4%)	8(34.8%)	2(8.7%)	23(100%)	
Total occlusion	11(73.3%)	0(0.0%)	0(0.0%)	4(26.7%)	15(100%)	
Total	25(47.2%)	10(18.9%)	12(22.6%)	6(11.3%)	53(100%)	

* significant (P value ≤0.05), figures in the parentheses indicate correspondingpercentage;
Chi-squared (χ^2)Test was done to analyze the data.

Table-IV

Distribution of territory of infarction according severity of stenosis (n=25)

Territory of Infarct	Severity of Stenosis			Total (n=25) No. (%)	p-value
	Moderate stenosis (n=5) No. (%)	Severe stenosis (n=9) No. (%)	Total occlusion (n=11) No. (%)		
ACA	1(20.0%)	0(0.0%)	0(0.0%)	1(4.0%)	0.247^{ns}
MCA	4(80.0%)	9(100.0%)	10(90.9%)	23(92.0%)	
PCA	0(0.0%)	0(0.0%)	1(9.1%)	1(4.0%)	
Total	5(100.0%)	9(100.0%)	11(100.0%)	25(100.0%)	

ns: significant (P value > 0.05), figures in the parentheses indicate correspondingpercentage;
Chi-squared (c^2)Test was done to analyze the data.

Discussion:

Total 53 ischemic stroke patients with significant symptomatic stenosis of ICA were studied. Analysis of age distribution showed that mean age was 58.83±9.85 years with range from 35-77 years. 60-69 year group was seen most commonly encountered (41.5%). There was no significant association found between age of the study population and location of stenosis. An epidemiological survey of stroke in Bangladesh[15] revealed that highest prevalence of stoke was among 65-79 years of age. Another DSA based study[16] from BSMMU revealed mean age was 61.55 ± 8.85 years with 60-69 year group being most commonly (42.9%) encountered. Another DSA based study[17] among diabetic patients revealed mean age was 57.9 ± 9.2 years. A study[18] in India found mean age 57.97 ± 10.75 years with most commonly affected patients were above 60 years of age and no association between stenosis and age. These results are almost similar to our study.

In our study, among 53 patients, 35 were male and 18 were female with male female ratio 1.51:1. There was no association found between sex of patient and location of stenosis. A study[15] revealed that male female ratio was 1.94:1. In another DSA based study[19] found male female ratio was 1.65:1. The reason behind this discrepancy in male female ratio may be explained by increased incidence of stroke in male and also negligence of female ischemic stroke patients.

Our study with 53 patients revealed, 15(28.3%) patients had moderate stenosis, 23(43.4%) patients had severe stenosis and 15(28.3%) patients had total occlusion of ICA. In a recent study at BSMMU[16], moderate, severe and total occlusion were observed in 26.2%, 40.5% and 33.3% respectively among 42 patients.

In our study among 53 ICA stenotic segments, 84.9% were in cervical segment, 7.5% were in cavernous segment and 7.5% were in supraclinoid segment. No patient had stenosis in petrous part. The total occlusion of ICA was always observed in cervical segment. Among 45 patients with stenosis of cervical segment of ICA, 53.3% had territorial infarct, 17.8% had lacunar infarct, 15.6% had subcortical infarct and 13.3% had watershed infarct. Among 4 patients with stenosis in cavernous part 50.0% had subcortical and 50.0% lacunar infarct. And among 4 patients with supraclinoid stenosis 75.0% had lacunar and 25.0% had territorial infarct. This observation was statistically significant.

A study[20] of large vessel atherosclerotic cerebrovascular disease revealed among 277 patients with ICA disease, 91.7% had cervical segment involvement and 8.3% had intracranial involvement. Total occlusion was observed in 82 patients among them 95.1% had occlusion in cervical segment. Another study[21] about infarct volume and pattern of ICA disease revealed that, among 47 patients 48.9% presented with watershed zone infarct, 14.9% with subcortical

infarct, 14.9% with lacunar infarct and 10.6% with large territorial infarct. A study[22] comparing infarct pattern between MCA and ICA disease revealed that, among 63 patients with ICA disease 27% had lacunar infarct and 73% had territorial infarct. Another study[23] of 31 patients with severe to total occlusion of ICA revealed 67.7% had territorial infarction and 32.3% had watershed zone infarct. These studies revealed almost same findings as ours.

We found significant difference between subtype of infarct and severity of stenosis (p-value = 0.003).Among 15 patients with moderate stenosis of ICA, 66.7% presented with subcortical or lacunar infarction and 33.0% presented with territorial infarction. In case of severe stenosis, territorial, lacunar and watershed infarct were 9(39.1%), 8(34.8%) and 2(8.7%) respectively. Whereas total occlusion of ICA presented as either territorial infarction (73.3%) or watershed infarction (26.7%). An MRI based study[8] about acute ischemic stroke pattern revealed, among 19 patients with moderate stenosis 36.8% had lacunar infarct and 26.3% had subcortical infarct. Among 41 patients with severe stenosis, 51.2% had watershed infarct and 26.8% had territorial infarct and among 42 patients with total occlusion, 61.9% had territorial infarct and 21.4% had watershed zone infarct. Another study[23] of 31 patients with ICA stenosis of 70% or more revealed 67.7% had territorial infarction and 32.3% had watershed zone infarct. In another large study[24] among 413 ischemic stroke patients with ICA disease, 33.4% had lacunar infarct and 26.2% had watershed zone infarct. They also showed that 63% of watershed infarct was encountered in ICA stenosis of 70% or more, whereas 42% of such patients presented with lacunar infarct.

Among 53 patients with ICA stenosis, we found 25 patients with territorial infarction. 92.0% had infarction in MCA territory, 4.0% had infarction in PCA territory and 4.0% had infarction in ACA territory. A large study[25] revealed that MCA was the most frequently involved territory (49.6%) and PCA was involved in (8.5%). Another hospital-based study of young patient with ischemic stroke[26] revealed 21.86% had large artery stenosis among them 77.7% had MCA territory infarct. A DSA based study[27]from India revealed, among 161 patients, 81.5% had MCA territory infarction, 4.35% had PCA and 1.2% had ACA territory infarction. Another study[28] about the etiology of MCA territory infarct showed that, 40% ICA occlusion was found among MCA territory infarct.

Conclusion:

The present study revealed that, ischemic stroke patients had more cervical segment of ICA involvement than intracranial part of ICA. Territorial infarction was more commonly associated with severe stenosis and lacunar stroke was more commonly associated with moderate stenosis. Watershed infarction was an indicator of severe stenosis.

Ethical issues:

All patients gave informed written consents and the study was approved by Institutional Review Board of Bangabandhu Sheikh Mujib Medical University.

Conflict of interests:

The authors declare that they have no conflict of interest.

Abbreviations

ACA: Anterior Cerebral Artery, BSMMU: Bangabandhu Sheikh Mujib Medical University, CTA: Computed Tomography Angiogram, DSA: Digital Subtraction Angiography, ICA: Internal Carotid Artery, MCA: Middle Cerebral Artery, MRA: Magnetic Resonance Imaging, NASCET: North American Symptomatic Carotid Endarterectomy Trial, PCA: Posterior Cerebral Artery, SD: Standard Deviation, TOF: Time of Flight MRI.

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Bangladesh Journal of Neuroscience 2019; Vol. 35 (2): 78-85

Prognostic significance of Intracerebral Hemorrhage Score in predicting 30-day mortality in Chittagong Medical College Hospital

EMRAN MS[1], HASSANUZZAMAN M[2], MAJUMDER S[3], ISLAM MRT, KABIR MHU, SIKDER ABMNHV, MAJUMDER PW, UDDIN SAX , RUBEL MY, RAHMAN MW[10],CHOWDHURY MAA[11], KHAN MA[12], SARKER MHK[13], CHOWDHURY A[14]

Abstract:

Background:*Prognosticating the outcome of Intracerebral Hemorrhage (ICH) at the time of admission is important to customize treatment in a cost-effective manner in such cases. ICH sore is a widely used prognosticating tool but yet not evaluated in our setting. This study was aimed to assess the prognostic factors influencing outcome and validating the ICH score for prediction of 30-day mortalityin hospitalized patients with ICH.* ***Materials and methods:****This prospective observational study was conducted in Chittagong Medical College Hospital, Bangladesh among 105 consecutively admitted patients aged 18 years and above with a computed tomography evidence of spontaneous ICH. ICH score was calculated soon after confirmation of diagnosis. Primary outcome measure was 30-day mortality after admission. Modified Rankin Scale (mRS) was used to assess outcome at discharge and at 30-day follow up.* ***Results:****A total of 104 patients were analyzed. Mean age of this cohort was 59.30±19.91 years. At 30 days all 27 patients with an ICH score of 0 survived, whereas those having scores of 1, 2, 3, and 4 had 5.9%, 33.3%, 46.2% and 88.9% mortality, respectively. ICH score was good for discriminating 30-day mortality with having an area under the ROC curve of 0.886 (95% CI:0.816-0.956; p<0.001]. For patients scoring above 2, the rate of poor functional outcome (mRS score e"4) approaches 100%. On the other hand, 18.5% of patients with score of 0 and 64.7% of patients with a score of 1 are not functionally independent after 30 days.* ***Conclusion:****In conclusion, the present study has demonstrated that the ICH score is a strong prognostic indicator of ICH outcomes (30-day mortality and 30-day functional outcome) among hospitalized patients in Bangladesh.*

Key words:*Intracerebral Hemorrhage; Intracerebral Hemorrhage Score; Prognosis; Bangladesh.*

Background:

Intracerebral hemorrhage (ICH) is the second most common cause of stroke and accounts for 10-20% of all strokes[1,2]. The incidence of ICH is increasing over the years[3] and ICH remains the most dreadful among stroke subtypes with a 30-day mortality of 40%–50%[4]. Though the exact scenario of Bangladesh is not known due to scarcity of

1. Dr. Md. Shawkat Emran, Resident, Department of Neurology, Chittagong Medical College, Chattogram, Bangladesh. Email: dr.emran13comc@gmail.com
2. Dr. Md. Hassanuzzaman,Professor and Head, Department of Neurology, Chittagong Medical College& Hospital, Chattogram.
3. Dr. ShiulyMajumder,Associate Professor, Department of Neurology, Chittagong Medical College& HospitalChattogram.
4. Dr. Md. Rafiqul Islam, Professor, Department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.
5. Dr. Md. HumayunKabir,Neurologist, Chittagong Medical College Hospital.
6. Dr. Abu Bakar Muhammad NizamulHoqueSikder, Resident, Department of Neurology, Chittagong Medical College.
7. Dr. PijushMajumder, Registrar, Department of Neurology, Chittagong Medical College Hospital.
8. Dr. Syed ArifUddin, Resident, Department of Neurology, Chittagong Medical College.
9. Dr. Md. Rubel, Resident, Department of Neurology, Chittagong Medical College.
10. Dr. Md. WahidurRahman, Resident, Department of Neurology, Chittagong Medical College.
11. Dr. Mohammad AnwarulAzimChowdhury, Resident, Department of Neurology, Chittagong Medical College.
12. Dr. Md. Ashrafuzzaman Khan, Neurologist, National Institute of Neurosciences & Hospital (NINS&H), Dhaka.
13. Dr. Md. HumayunKabirSarker, Resident, Department of Neurology, Dhaka Medical College.
14. Dr. Ashish Chowdhury, Resident, Department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU).

published literature it can be assumed that, the incidence of ICH is higher in comparison to the western population[1,5], and the population at risk is younger compared to the western developed world[6]. Considering the poor long-term outcome for spontaneous ICH patients, an effective prognosticating scale is important to optimize the management plan for careful use of available resources, especially in low to middle income countries[7]. The ICH score is one of the simple and functional methods in this regards.It is determined as the sum of specific point values for each of the five characteristics (GCS score, age e"80 years, ICH volume, presence of IVH, and infratentorial origin), with weighting of potential points for each characteristic based on strength of outcome association[8].

However, for wider applicability of a risk-stratification scale, such as the ICH score, it must be useful outside the cohort of patients from which it was developed. So, external validation to determine whether the ICH score could accurately risk-stratify patients in a cohort independent of that from which it was developed was done in different population. Till date several studies in abroad have shown the external validity of ICH score but the study population and the hospital settings were completely different from ours[6,9-14]. Published study on ICH score in Bangladesh is very limited and the external validity of ICH score is not aimed in any study yet. So, it is necessary to prove its efficacy as a predictor of adverse outcome of ICH in Bangladeshi population.

Contemplating this background, this study was planned to evaluate the role of ICH score in predicting 30-day mortality in patients with ICH presenting and getting admitted in a tertiary care hospital of Bangladesh.

Materials and methods:

This prospective observational study was performed in Chittagong Medical College Hospital, Chattogram, Bangladesh. It is a 1313 bedded tertiary care hospital and one of the largest hospitals in Bangladesh. Patients with ICH are usually admitted in different Medicine, Neurology and Neurosurgery wards of this hospital.

All patients with a computed tomography (CT) evidence of spontaneous ICH above the age of 18 years were included in this study. Patients or attendantswho denied formal consent, patients with coagulation abnormalities, aneurysmal hematomas, and vascular malformations,past history of stroke, patients having ICH secondary to a brain tumor or trauma, patients with a past history of stroke and patients who were undergone surgical procedure were excluded.

Sample size was determined for the comparison of the area under a Receiver Operating Characteristics Curve (ROC) curve. A sample of 71 patients would suffice for a 90% power to detect a difference of 0.3 between the area under the curve (AUC), under the null hypothesis of AUC = 0.5 (no diagnostic accuracy) and the alternative hypothesis of AUC = 0.8 (moderate diagnostic accuracy), at a significance level of 0.05. However, considering the lost to follow up and to further increase the power of the study finally 105 patients were included in the study

Patients with a suspected diagnosis of acute stroke were subjected to an urgent noncontrast CT scan of the brain as soon as possible. Soon after, those diagnosed as ICH was enrolled and physically examined along with an evaluation for ICH scores. The scores used for 30-day mortality prediction was based on the ûrst evaluation after the enrollment. The data of the study subjects was collected by oral questionnaire regarding age, sex, education level, and risk factors for ICH (hypertension, diabetes, alcoholism, smoking, and anticoagulant and antiplatelet medications). Pulse, blood pressure (BP), respiratory rate, temperature, and GCS score was noted on admission. Hypertension and diabetes was diagnosed as having a previous diagnosis of these conditions by a registered physician or patients on anti-hypertensive or anti diabetic medications. Smoking was defined ever or never smokers. Obesity was defined as waist circumference >90cm in males and >80cm in females. Poor functional outcome was defined as mRS score e"4 at 30 days.As it was an observational study, the treatment protocol of the patient had not been interrupted and he/she had got the treatment as per available hospital protocol.

Patients of the study were monitored until discharge or death to observe the outcome. For those who had died within 30 days during the hospital stay, the cause of death was documented from the case record files. Those who was discharged before 30 days, a follow-up visit was arranged after 30 days of admission. Some patients who failed to attend the follow-up visit, telephonic follow-up was done.Primary outcome was defined as mortality assessment at 30-day after ICH. A patient who survived and discharged was followed up in the outpatient department and over telephone regarding their final outcome.

Continuous data were expressed as mean ± standard deviation (SD) and categorical variables were presented as percentages or proportions. The entire cohort was divided into survivor and non-survivor groups. Between these two groups, continuous and categorical variables were analyzed. Student's t-test was used to analyze continuous variableswhile categorical variables were compared by means of Chi-square test. Multivariate analysis, with the 30 day mortality as dependent variable, on variables found to be significant by univariate analysis, was performed finally. The discriminatory values of ICH score for predicting 30-day mortality was studied using ROC curve analyses with calculation of AUC. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 23.0.

Informed consent was obtained from competent patients before enrollment. In patients who were unable to give fully informed consent, assent was obtained from a legal representative. The study protocol was approved by the Ethical Review Committee of Chittagong Medical College (Memo number: CMC/PG/2019/543) on June 20, 2019.

Results:

Out of 105 enrolled patients one was lost to follow up and rest 104 were included in the final analysis. Out of 104 patients 81 patients survived and rest 23 died in 30 days following enrollment. Overall, the mean age of the study subjects was 59.3 years and there was female predominance. In univariate analysis, mean age (p=0.04) but not the age group of e"80 years was significantly associated with 30 days mortality. (Table I). Majority of the patients were hypertensive (76%) and about half of them were obese (49%). However, DM, IHD alcohol drinking habit, smoking and tobacco leaf use was present in 16.3%, 19%, 1.9%, 36.5% and 27.9% respectively. There was no association of these factors with 30-day mortality.The frequency of IVH, hydrocephalus and hemorrhage with a volume of 30 cc or higher were significantly higher among the subjects who died ($p<0.05$).Those who survived had a higher GCS than those who died, the difference being statistically significant ($p<0.001$).In this cohort only 8.7% patients had infratentorial ICH and it was not associated with 30-days mortality (Table I.

In this cohort of 104 patients with ICH, 34 (32.7%) patients had ICH score 1. No patients had ICH score 5 and above (Table II). Present study demonstrated that, 30-day mortality increases as ICH Score increases. No patient with an ICH Score of 0 died. Majority of patients (88.9%, 8/9) with an ICH Score of 4 died. The 30-day case fatality for the entire cohort was 22.1% (23/104; 95% CI, 14.13%–30.07%).

Figure 1 contrasts the "observed mortality" vs "expected mortality" as predicted by the ICH Score. Mortality increased with ICH score, but not to the extent previously reported. In particular, the largest discrepancy between observed and expected mortality was demonstrated among patients with ICH Scores of 3 (46% vs 72%, $P<0.01$).

The areas under ROC curve for the ICH score was 0.886 (95% CI: 0.816-0.956; $p<0.001$) (Figure 2). The ROC suggested a sensitivity of 90% at cutoff value of 3 with specificity of 71%.

In the present cohort, ICH score was found to be predictive of poor functional outcome (mRS score $\geq$4) at 30 days after discharge. From Figure 6 it is apparent that for all patients scoring above 2, the rate of poor functional outcome approaches 100%. On the other hand, 18.5% of patients with score of 0 and 64.7% of patients with a score of 1 are not independent after 30 days.

Variables that had a p value of <0.05 in univariate analysis were selected for the multivariate regression analysis (Table 3). GCS score, the

Table-I

Socio-demographic variables of the 104 patients with ICH and association of 30-day mortality with these variables

Variables	Total (n=104)	Survival (n=81)	Death (n=23)	p value
Age (years)				
<80	93 (89.4%)	75 (80.6%)	18 (19.4%)	0.063*
≥80	11 (10.6%)	6 (54.5%)	5 (45.5%)	
Mean ±SD	59.30±19.91	57.91±12.79	64.17±12.69	0.040†
Sex				
Female	56 (53.8%)	45 (80.4%)	11 (19.6%)	0.512‡
Male	48 (46.2%)	36 (75.0%)	12 (25.0%)	
Risk factors				
Hypertension	79 (76.0%)	63 (79.7%)	16 (20.3%)	0.480‡
Diabetes mellitus	17 (16.3%)	12 (70.6%)	5 (29.4%)	0.430*
Obesity[a]	51 (49.0%)	41 (80.4%)	10 (19.6%)	0.546‡
IHD	2 (1.9%)	1 (50.0%)	1 (50.0%)	0.368*
Smoking	38 (36.5%)	28 (34.6%)	10 (43.5%)	0.289‡
Tobacco leaf use	29 (27.9%)	23 (28.4%)	6 (26.1%)	0.998‡
Alcohol drinking	2 (1.9%)	1 (50.0%)	1 (50.0%)	0.368*
GCS				
13-15	54 (51.9%)	51 (94.4%)	3 (5.6%)	<0.001*
5-12	46 (44.2%)	30 (65.2%)	16 (34.8%)	
3-4	4 (3.8%)	0 (0%)	4 (100%)	
Hematoma volume				
<30 cc	75 (72.1%)	66 (88.0%)	9 (12.0%)	<0.001‡
e”30 cc	29 (27.9%)	15 (51.7%)	14 (48.3%)	
Location				
Supratentorial	95 (91.3%)	75 (78.9%)	20 (21.1%)	0.402*
Infratentorial	9 (8.7%)	6 (66.7%)	3 (33.3%)	
IVH[a]	45 (43.3%)	27 (60.0%)	18 (40.0%)	<0.001*
Hydrocephalus	9 (8.7%)	3 (33.3%)	6 (66.7%)	0.003*

Data are expressed as frequency (percentage) if not mentioned otherwise. *p value derived from Fischer’s exact test; ‡ p value derived from Chi-square test; †p value derived from Student’s t-test; Significant values are in bold face.IVH; Intraventricular hemorrhage.

Table-II

30-days mortality rate for the Entire Cohort of 104 patients with ICH and Stratified by ICH Score

ICH score	n (%)	Case fatality rate at 30-day, n (%)	95% Confidence intervals
0	27 (25.9%)	0 (0%)	0-0
1	34 (32.7%)	2 (5.9%)	0.02-13.82
2	21 (20.2%)	7 (33.3%)	13.14-53.46
3	13 (12.5%)	6 (46.2%)	19.09-73.30
4	9 (8.7%)	8 (88.9%)	68.38-100
Entire cohort	104 (100%)	23 (22.1%)	14.13-30.07

Table-III

Multivariate logistic regression analysis of predictive 30-days mortality in 104 patients with ICH

Variables	β	Odds ratio (OR)	95% CI of OR		P value
			Lower	Upper	
Age	0.037	1.04	0.98	1.09	0.196
GCS	-0.398	0.67	0.52	0.86	0.002
Hematoma volume (≥30 cc)	1.565	4.78	1.23	18.57	0.024
IVH	0.084	1.09	0.24	4.98	0.914
Hydrocephalus	2.111	8.25	1.11	61.24	0.039

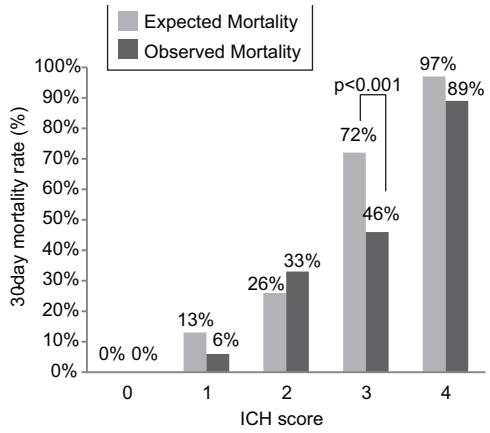

Fig.-1: *30-day mortality rate by presenting ICH score (Blue bars show expected mortality rate based on the original ICH score. Red bars show observed mortality rates in our patient cohort. Significant differences were seen between patients with ICH scores of 3).*

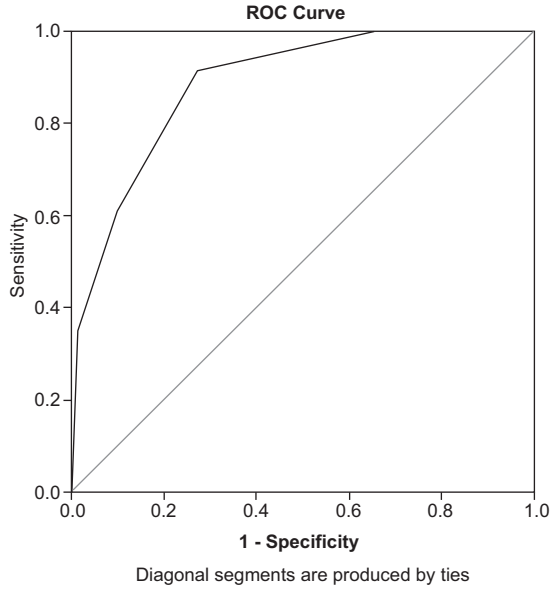

Fig.-2: *Receiver operating characteristic (ROC) curve for ICH score in predicting 30-day mortality outcome.*

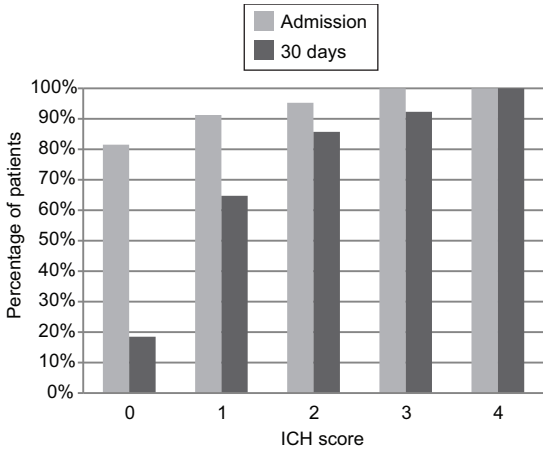

Fig.-3: *The ICH score and proportion of patients with modified Rankin score of e"4 at admission and one month after discharge.*

hematoma volume (≥30 cc), and the presence of hydrocephalous were independent predictors of 30-daymortality (p = 0.002, p=0.024 and p=0.039 respectively).

Discussion:

In this prospective study in Bangladesh, we have demonstrated that the ICH score is a valid prognostic indicator of 30-day case fatality. The overall 30-day mortality rate in the present cohort was 22.1%. When stratified by ICH scores, the mortality rate was significantly lower than the predicted mortality, which has been previously reported, in patients with ICH score 3. The observed mortality rate in the present study was similar to that predicted in Hemphill's ICH score for the other ICH scores[8]. Historically quoted 30-day mortality rates of 72% for scores of 3 were based on a sample size of 32 patients for ICH score of 3 in the original cohort where the ICH score was

developed[8]. In our patient population, the total number of patients with an ICH Score of 3 was only 13, of which 6 died (mortality rate of 46.2%). Difference in the sample sizes might be responsible for these differences in the observed and expected mortality rate between original and present study cohort.

The pattern and demography of spontaneous ICH in Bangladesh is different from the western world but quite similar to our neighboring country India. The mean age of the patients in the present study was 59.30 (±19.91) years, which is predominantly younger in comparison to the western population where the mean age was 70–79 years[8,9,15]. However, most of the available studies from Bangladesh and India report mean ages of 55-65 years[6,14,16]. Only 10.6% patients were above the age of 80 in the present study. The United Nations report states that the average life expectancy of a Bangladeshi at birth is 72.72 years[17]. Thus, most of our population fail to live beyond the age of 80 which is one of the cutoff criteria for the existing ICH scoring system. This was evident from our observation that none of the patients in this study group had an ICH score of 5. In the present study male to female representation was almost equal (46.2% versus 53.8%). Several other studies also observed such non-significant gender differences[14,18]. Hypertension was the most prevalent risk factor in the current cohort(76%) followed by obesity (49%). IHD, smoking, and alcohol abuse were less prominent risk factors in the present study. This pattern was more or less similar to the findings from the study in and around our country[19,20].

The 30 day mortality of patients with spontaneous ICH has been reported as ranging from 25 to 52%[10,21,22]. The low rate at 22.1% in our study might be explained by our exclusion criteria. Patients with an initial absence of brainstem reflexes in whom the non-treatment concept was clear were not included in the study group. Concerning the short term outcome (after 30-days), 21 (20.19%) patients had mRSscore d”2 (slight disability to no symptom at all) and 66 (63.46%) had mRS score ≥4 (moderately severe disability to dead). In a meta analysis, Van Asch et al. presented a functional outcome with independency rates of between 12 and 39% corresponding to the findings of present study[23].

Multivariate analysis of the components of ICH score in our study subjects revealed that GCS and hematoma volume (e”30cc) were strong predictors of 30-day mortality. However, the infratentorial origin of hemorrhage and IVH despite having high odds for death was not signiûcantly associated with the mortality prediction, which is in contradiction with the previous studies[8,24]. This discordance could possibly be due to very small number of patients having infratentorial hemorrhage (8.7% infratentorial versus 91.3% supratentorial), which could not reach statistical signiûcance. Most of the patients with IVH in the present study had associated hematoma volume of e”30 cc. So, the IVH was not revealed as an independent predictor of 30-day mortality though this variable had highly significant association (p<0.001) with 30-day mortality in univariate analysis. Age 80 years or older was an independent predictor of mortality in the original study of the ICH score[8]. The lack of association between age of 80 years or older and mortality in the present study may be due to the small number (11/104; 10.6%) of patients older than 80 years.

The present study also demonstrated that, the radiological feature hydrocephalus was an independent predictor of 30-day mortality. Diringer et al. demonstrated for the first time the impact of hydrocephalus on outcome from ICH[25]. Hydrocephalus was associated with a considerably higher mortality and fewer patients being discharged to home in their study. In agreement to our study, univariate and multivariate analyses indicate that hydrocephalus was an independent predictor of outcome in that study [25]. Later on, this factor is validated by other study[6].

The Hemphill ICH score has been validated numerous times in the literature, with a pooled AUC of 0.8 in an international meta-analysis[26]. In the present study the AUC for the ICH score was 0.886 (95% CI: 0.816-0.956; p < .001) which was consistence with other studies[26].

The results of the present study also support the validity of the ICH score in predicting early functional outcome in addition to mortality. This is consistent

with the study of Jamoraet al[11]. But in disagreement with the study that have evaluated outcome too early at discharge without accounting for the eventual improvement in function over time[12].

Strength and limitations:The strengths of our study include the prospective nature of the data collection and the blinding of image analysis and prognostic score determination to survival status. ICH grading scores are not routinely used for clinical care at our hospital and were determined retrospectively for this study, thus preventing them from influencing care decisions and, hence, prognosis. We were able to ascertain the outcome status of almost all of the patients with otherwise complete data and only 1 out of 105(<1%) could not be traced. However, lack of long-term follow-up of patients after discharge from the hospital and sample from a single hospital were some of the limitations of the present study. Moreover, we could not establish the true strength of association of infratentorial origin of hemorrhage and age e"80years because of the small number of subjects in these respective categories.

Conclusion:In conclusion, our study has demonstrated that the ICH score is a prognostic indicator of ICH for both30-day mortality and 30-day functional outcome among hospitalized patients in Bangladesh.A numerical scoring system like ICH score can improve the consistency among the physicians regarding severity of ICH which in turn can help during counseling the caregivers.

Recommendations:As the ICH score was observed to have a good discriminative power for predicting 30-day mortality in patients with ICH, present study recommended routine assessment of ICH scores in patients with ICH in admission. However, results of the current study need to be confirmed by further prospective, multicenter studies with larger sample size.

Acknowledgement:
Dr. Pradip Kumar Kayasthagir, Dr. Md. Mahabubul Alam Khandker, Dr. S A M Masihuzzaman (Alpha), Dr. TouhidurRahman, Dr. Zaman Ahmed, Dr. AnwarulKibria, Dr. AkramulAzam, Dr. FaridUddin Ahmed, Dr. Sanjay Saha.

Contribution of authors:
MSE: Conception, designing, data collection, data analysis, manuscript drafting & final approval

MH: Conception, Manuscript drafting & final approval

SM: Manuscript drafting & final approval

Conflict of Interests: The authors declare no conflict of interest in this study.

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Bangladesh Journal of Neuroscience 2019; Vol. 35 (2): 86-94

Impact of Risk Factors on the Size of Ruptured Intracranial Saccular Aneurysms

SARKER MHK[1], HABIB M[2], SHAHIDULLAH M[3], DEY SK[4], ISLAM S[5], ISLAM MR[6], DEY SK[3], AHMED KGU[7], CHOWDHURY AH[6], SHAHALY S[7], ROY LK[1], HASAN MH[1], EMRAN MS[8], CHOWDHURY A[9], AKTER S[1], HASAN M[9], ABIR K[1]

Abstract:

Background: *Un-ruptured intracranial aneurysms (UIAs) are common and prevalence is about 2 to 8%. Several studies have shown that the decision to treat un-ruptured aneurysms should not be based on aneurysm size alone. A study suggest that treatment of UIAs smaller than 7 mm in hypertensive patients and smokers may be beneûcial.* ***Aim and objective:*** *The goal of this study is analysis of correlation of age, gender, location of the aneurysm, history of hypertension and cigarette smoking, previous history of SAH with the size of ruptured aneurysms.* ***Materials and Methods:*** *This hospital based observational cross-sectional study was conducted in the Department of Neurology & Neurosurgery, Dhaka Medical College Hospital (DMCH), Dhaka. Total 44 patients with SAH were taken by inclusion & exclusion criteria. The aneurysms size, site of location and aneurysm multiplicity was assessed by three-dimensional rotational digital subtraction angiography (DSA).* ***Results:****The mean age of the study population was 49.24 ±11.5. About half of the population were within 51-60 years. The male female ratio was 1:1.2. Out of 44 population, 93.2% were presented with headache, 90.9% with vomiting. In this study aneurysms mean size was 5.72±4.010 mm. 93.2% of aneurysms were below 10 mm, 75.0% were below 7 mm and 50.0% below 5 mm. Size of ruptured aneurysm is small in hypertensive population and is significant (p-value 0.037). Aneurysm size was significantly (p- value 0.013) smaller in case of smoker. Mean aneurysm size in hypertensive smoker population was significantly (p-value-0.004) smaller than hypertensive non-smoker. Population with one risk factor had mean aneurysm size was 8.32±6.84 mm, two risk factors had 5.26±1.86mm, three risk factors had 4.79±2.05 mm and more than three risk factors had 2.85±1.43.* ***Conclusion:*** *This study shows that more the risk factors, smaller the size of aneurysms. Therefore, history of hypertension, cigarette smoking, female sex, age and positive family history should be considered in the assessment of treatment of un-ruptured intracranial aneurysms.*

Key words: *SAH, risk factors, intracranial Aneurysms, aneurysms size*

Introduction

Subarachnoid haemorrhage (SAH) is one kind of stroke, measuring 1 to 7% of stroke patients. SAH is responsible for 5% of stroke death[1]. Incidence of SAH is approximately 6-15 per 100,000 people per year[2]. Up to 50% of all cases of SAH are fatal and 10-15% die before reaching hospital[3]. After hospital admission one-third will die, about one-

1. **Md. Humayun Kabir Sarker,** Resident, Department of Neurology, Dhaka Medical College, Dhaka, correspondence-himu33bd@gmail.com.
2. Professor Dr. Monsur habib and Head (Rtd), Department of Neurology, Dhaka Medical College, Dhaka
3. Dr. Md. Shahidullah,Associate professor**,** Department of Neurology**,** Bangabandhu Sheikh Mujib Medical University (BSMMU)
4. Dr. Shuvash Kanti Dey, Associate professor**,** Department of Neurology**,** Bangabandhu Sheikh Mujib Medical University (BSMMU)
5. Dr. shafiqul IslamAssociate professor**,** Department of Neurosurgery**,** Dhaka Medical College
6. Professor Dr. **Md. Rafiqul Islam**, Department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka
7. Dr. **Kazi Gias Uddin Ahmed[6],** Associate Professor, Department of Neurology, Dhaka Medical College, Dhaka.
7. Resident, Department of Physical Medicine and Rehabilitation, Dhaka Medical College, Dhaka
8. Resident, Department of Neurology, Chittagong Medical College, Chittagong
9. Resident**,** Department of Neurology**,** Bangabandhu Sheikh Mujib Medical University (BSMMU)

third will recover with severe disability and about one-third will have excellent recovery [4]. Those who survive often have neurological and cognitive impairment [3]. The economic impact of SAH is severe because it mostly affect the patients in 40s and 50s during their most productive years[5]. Though incidence of SAH in Bangladesh is unknown. In Kashmir, India the incidence of SAH is 13/100000[6]. Bangladesh is culturally, religiously almost same as Kashmir.

Cerebral aneurysms are the most common cause of non-traumatic subarachnoid hemorrhage and is responsible for 70 to 75% of spontaneous SAH[7]. Ruptured "Berry" aneurysm is the most common among the aneurysmal SAH and is responsible for 85% of cases[8].

In a univariate analysis, family history of SAH, systemic hypertension, cigarette smoking and regular alcohol consumption were significant risk factors for aneurysmal SAH. In a multivariate analysis, after adjustment for other risk factors, family history of SAH, cigarette smoking and hypertension remained significant[9].

Size of intracranial aneurysm is a key prognostic factor for rupture[10]. In general large aneurysms are more likely to rupture[11-15]. One large, multicenter trial suggested that aneurysms 10 mm or larger had a 1% annual risk of rupture, with smaller aneurysms having a much smaller risk of rupture. There seems to be a general agreement that the unruptured aneurysm e" 10mm in diameter should be treated surgically[16]. Recent studies, including the prospective arm of the International Study of Un-ruptured Intracranial Aneurysms (ISUIA) suggest that aneurysms smaller than 10 mm have higher rates of rupture than previously predicted[17].

Age and sex also influences on size of aneurysms [18,19].Site of aneurysm also impact on size of ruptured intracranial aneurysms (RIAs) [20,21]. The size at which aneurysms rupture appears to be smaller in those patients with the combination of hypertension and smoking than in those with either risk factor alone [22].

Recently, unruptured intracranial aneurysms (UIAs) are increasingly detected due to the increased availability and improved sensitivity of noninvasive imaging technique[23]. Unruptured intracranial aneurysms (UIAs) are common, with autopsy studies placing their prevalence at approximately 2 to 8% [24,25].

The ISUIA 2 study concluded that aneurysms < 7 mm in size in the anterior circulation have an annual rupture risk of 0-0.1% per year [16]. But there are many studies that contradict with this study. The natural history of small un-ruptured aneurysms (<5 mm in diameter) without surgical treatment and found that the annual rupture rate was 0.8% for 380 aneurysms followed up for a mean of 13.8 months [26]. The annual bleeding rate was 1.92% [27], 1.3%[28], 1.5[29] and 2.3%[30].

Several studies have shown that the decision to treat un-ruptured aneurysms should not be based on aneurysm size alone [31-34]. A study suggest that treatment of UIAs smaller than 7 mm in hypertensive patients and smokers may be beneûcial [22].

The aim of this study is to find out the effect of risk factors on size of ruptured aneurysms, to assess the critical size at which most of aneurysms ruptured. So that we can able to draw a conclusion that a critical sized un-ruptured aneurysms with risk factors should consider either microsurgery or coiling.

Materials and Methods:

This was an observational, cross-sectional study. Forty four patients with aneurysmal subarachnoid haemorrhage admitted in Department of Neurology and Neurosurgery, Dhaka medical college hospital (DMCH) were included for the study following proposed inclusion and exclusion criteria.

Following admission, patients with SAH was diagnosed clinically and was confirmed by CT scan of head or by lumber puncture (LP) in CT scan negative cases. Non-Aneurysmal SAH, Other than saccular aneurysms (Fusiform, traumatic and mycotic aneurysm) and arterio-venous malformation associated aneurysm were excluded.

A written informed consent was taken from each patient or their guardians. History regarding demographic profile (age, sex, marital status, education, socioeconomic level, family details); risk

factors (hypertension, prior history of SAH, smoking habit & alcohol, drug abuse) and clinical presentation was noted on the questionnaire.

The aneurysm size, site of location and aneurysm multiplicity was assessed by three-dimensional rotational digital subtraction angiography (DSA).

The location of the aneurysm was classified as follows: A) anterior circulation and B) posterior circulation. Multiplicity of aneurysm is defined in this study as the occurrence of two or more than two aneurysms.

Smokers were divided into smoker and never smokers; current and past smokers were included as smoker. Patients who consumed alcohol were classiûed as heavy (30ml /day or more) or light drinkers (less than 30ml /day).

Hypertension was deûned if it had been diagnosed before admission. If systolic BP e”140 mm Hg and Diastolic BPe”90 mmHg was diagnosed as hypertensive.Hypertensive patients were divided into 2 groups, those who took antihypertensive medication regularly (medicated group) and those who either took it irregularly or not at all (poorly controlled group). Blood pressure readings at admission or during subsequent hospitalization was taken into account because it is considered to be reûective of initial or subsequent clinical conditions. A history of SAH was recorded separately from other cerebrovascular diseases (CVD) in both the patient's and his or her family medical history.

Hunt and Hess grading was recorded from patient history and examination. Subjects with incomplete data was excluded. The data was analysed using standard statistical procedures.

The statistical analysis was performed using SPSS software v. 26.0. Continuous parameters were expressed as mean±SD and categorical parameters as percentage. Differences between groups were analysed using Student t-test for metric variables and Chi-square test for ordinal or nominal scaled variables. The correlation between aneurysm size and risk factors were evaluated by one-way analysis of variance (ANOVA). Analysis of variance (univariate ANOVA) was among three groups. Statistical significance was defined as $p<0.05$ (CI% 0.95).

Results:

The study was conducted to assess the impact of risk factors on the size of ruptured intracranial aneurysms. Total 44 cases of subarachnoid hemorrhage were enrolled in this study. The mean age of the study population was 49.24 ±11.5. About half of the population were within 51-60 years.

Out of 44 population, 54.5% were female. The male female ratio was 1:1.2. Presentation of subarachnoid hemorrhage in this study was, 93.2% population were presented with headache, 90.9% with vomiting, 81.8% had neck stiffness, 52.3% were unconscious, 15.9% had seizure, and 15.9% hemiplegia. In this study 59.1% were hypertensive, 47.73% were smoker, 15.9% were alcoholic and were light drinker, 6.8% were substances abuser and 11.4% had positive family history of SAH. 43.2% of population were in Hunt and Hess scale 2. In this study, aneurysms mean size was 5.72±4.010 mm. According to International Study on Un-ruptured Intracranial Aneurysms (ISUIA), 65.9% aneurysm size were 3-7mm, 20.5% were 8-12 mm, 9.1% were below 3 mm.

Table-I

Distribution of the study patients by aneurysms size (n=44)

	Frequency	Percentage
<10 mm	41	93.2
>10 mm	3	6.8
<7 mm	33	75.0
>7 mm	11	25.0
<5 mm	22	50.0
>5 mm	22	50.0

In table-I, 93.2% of aneurysms were below 10 mm, 75.0% were below 7 mm and 50.0% below 5 mm.

Table-II

Aneurysm size relation with hypertension (n=44)

	Hypertension		
	Hypertensive (n=26) Mean±SD	Normotensive (n=18) Mean±SD	p-value
Aneurysm size (mm)	4.68±2.69	7.23±5.10	0.037

Table-II shows, size of ruptured aneurysm is small in hypertensive population and is significant (P value 0.037)

Table-III

Aneurysm size relation with smoking (n=44)

	Smoking status		
	Smoker (n=21)	Never smoker (n=23)	p-value
	Mean±SD	Mean±SD	
Aneurysm size (mm)	4.18±1.74	7.13±4.93	0.013

Table-III showsaneurysm size were 4.18±1.74 mm in smoker which is significantly (P value – 0.013) smaller than never smoker.

Table-IV

Aneurysm size relation with hypertension and smoking (n=26)

Hypertension	N	Mean±SD	p-value	
Yes	Smoker	14	3.36±1.35	0.004
	Never smoker	12	6.22±3.07	

Table-IV shows mean aneurysm size in hypertensive smoker population was 3.36±1.35 mm which is significantly (p-value-0.004) smaller than hypertensive non-smoker.

Table-V

Aneurysm size relation with presence of risk factors (n=44)

Risk factors	N	Mean±SD	p-value
One risk factor	11	8.32±6.84	0.063
Two risk factors	17	5.26±1.86	
Three risk factors	13	4.79±2.05	
> Three risk factors	3	2.85±1.43	

Table-V shows aneurysm size was dependent to presence of number of risk factors. More risk factors had small aneurysm.

Discussion:

The study was conducted to assess the impact of risk factors on the size of ruptured intracranial aneurysms. Total 44 cases of subarachnoid hemorrhage were enrolled in this study. The mean age of the study sample was 49.24 ±11.5 years. About half of the population were within 51-60 years. This is consistent with Reaz Mahmud et al where the average age was 48.24±9.26[35]. Another two studies conducted in Bangladeshthe mean age was 45.00±9.4 and 45.9 years[36,37].In an epidemiological study done in India had shown average age of subarachnoid hemorrhage in their population was 49.63 years[38].Worldwide the mean age of aneurysmal rupture is in the range of 50 to 55 years. The mean age of this study coincides with the both worldwide and sub-continent.

Subarachnoid hemorrhage (SAH) is a disease with definite female preponderance. In this study 54.5% were female. The male female ratio was 1:1.2. The ratios of men to women were constant at approximately 1.2:1[39], 1: 1.5[40] and 1:1.3[41]. A Bangladeshi study shows the male female ratio was 1:1.6[35].

93.2% population were presented with headache, 90.9% with vomiting, 81.8% had neck stiffness, 52.3% were unconscious, 15.9% had seizure, and 15.9% hemiplegia. According to a Bangladeshi study, headache, neck rigidity and vomiting was invariably (100%) complained by the patients at the onset. Two-thirds (66.7%) of the patients were unconscious at presentation and 10% exhibited cranial nerve palsy [36].

In this study 59.1% were hypertensive, 47.73% were smoker, 15.9% were alcoholic and were light drinker, 6.8% were substances abuser and 11.4% had positive family history of SAH. In Bangladesh a study of thirty SAH population revealed 44% of the patients had smoking habit and nearly half (46.7%) had hypertension [37]. Another study was

conducted at Dhaka medical college and Hospital showed hypertension, smoking, diabetes mellitus and family history of SAH were found in 46.6%, 43.3%, 10.0% and 6.7% respectively[42]. Presence of risk factors in study population were more or less same with Bangladeshi research. An international study showed hypertension was identified in 52% [24].

In this study, mean size of ruptured aneurysms was 5.72±4.010 mm. According to International Study on Un-ruptured Intracranial Aneurysms (ISUIA) classification, 65.9% aneurysm size were 3-7mm, 20.5% were 8-12 mm, 9.1% were below 3 mm. Many studies showed the mean size of aneurysms were 5.59±29mm[27], 6.6±2.7 mm[35], 5.8 mm[43], 5±1.9 mm [44] and 5.0 mm[45]. A total of 64 studies with 10873 intracranial aneurysms mean ruptured intracranial aneurysm size was 6.99 ± 4.14 mm[46]. The mean aneurysm size of this study is similar to findings in the national and international literature.

In this study shows 93.2% of aneurysms were below 10 mm, 75.0% were below 7 mm and 50.0% below 5 mm. About 91%[21], 80%[36], 85.6%[47] and 93.2%[48] were <10 mm in size. A study showed 75% of ruptured aneurysms <7 mm[48]. A study found 13% of the ruptured aneurysms they studied were less than 5 mm in diameter and 57% were between 5 and 10 mm in diameter[40]. More than half of the ruptured aneurysms measured less than 7 mm[48].In this study most of the aneurysms size were below 10 mm diameter which is similar to that of many literatures.

A study believes aneurysms shrink after rupture, so the calculated size of ruptured aneurysm does not reflect their size before rupture[17]. But there are lots of studies that established size of ruptured aneurysms do not change rather size increase [29, 49- 51].

In this study, 35.4% were ACom aneurysms, 29.2% were PCom aneurysms, 16.7% were MCA bifurcation. 87.5% aneurysms were in anterior circulation and 12.5% were in posterior circulation which is consistent with findings of both national and international publications [42, 52.]

In this study aneurysms size was smaller in older female patient which is consistent with Young-GyunJeong et al[18]. It is due to effect of estrogen hormone.

In this study mean aneurysm size in male was 5.67±3.09 mm and in female was 5.77±4.71 mm. Aneurysms size was 6.17 mm for males, and 5.91 mm for females[53]. A study showed gender-specific risk factor distribution did not differ significantly among males and females [22].

In this study mean aneurysm size were more in case of positive family history population. It is different from other literatures [18].This difference may be due to poor number of positive family history population in this study.

In this study mean aneurysm size was 4.68±2.69 mm in hypertensive patients and in normotensive population it was 7.23±5.10 mm. Size of ruptured aneurysm is small in hypertensive population and is significant (p-value 0.037). There was a significant correlation between hypertension and the rupture of aneurysms smaller than 5 mm[54].Hypertensive patients (6.27± 3.28 mm) had signiûcantly smaller ruptured intracranial aneurysms than normotensive (8.08±4.73 mm) [22].

In this study aneurysms mean size was 4.18±1.74 mm in case of smoker and 7.13±4.93 mm in never smoker. Aneurysm size was significantly (p- value 0.013) smaller in case of smoker. A study showed, patients with a history of cigarette smoking had only slightly smaller ruptured aneurysms (7.61±4.29 mm) compared to patients with no risk factors (8.08±4.73 mm) [22].

In this study mean size of aneurysm in male hypertensive population 5.04±3.57 mm which is smaller than male normotensive patient. In case of female hypertensive population mean size is 4.41±1.90 mm which is smaller than female normotensive patient and also from male hypertensive patient. In this study, male smoker had mean aneurysm size 4.65±1.79 mm which was significantly smaller than male never smoker (p-value 0.040) and in female smoker mean aneurysm size was 3.42±1.44 mm which was also smaller than female non-smoker and male smoker.

In this study mean aneurysm size in hypertensive smoker population was significantly (p-value-0.004)

smaller than hypertensive non-smoker. A study of 373 ruptured intracranial aneurysms and showed that the sizes of the ruptured IAs were significantly smaller in patients with a combined history of hypertension and cigarette smoking than those with hypertension alone, smoking alone or non-hypertension and non-smoking [22].

In this study population with one risk factor had mean aneurysm size of 8.32±6.84 mm, two risk factors had 5.26±1.86mm, three risk factors had 4.79±2.05 mm and more than three risk factors had 2.85±1.43. So, aneurysm size was dependent to presence of number of risk factors. More risk factors had smaller aneurysm which is consistent withNimaEtminan et al in which presence of one risk factor had smaller size than no risk factors and two risk factors had smaller size than one risk factor [22].

Conclusion:

The present analysis demonstrates that hypertension, smoking have a significant influence on the size of ruptured aneurysms in patients suffering from SAH. Other risk factors female sex, age, positive family history have also impact on aneurysm size but lesser extent. But when one risk factor is associated with other factors it decreases the size of ruptured aneurysm. In case of more the risk factors, the size become smaller. As a consequence, data strongly suggest that patients with these risk factors have a lower threshold of aneurysm rupture than patients without risk factors. Therefore, Size cannot be considered the only factor to determine treatment recommendations rather the history of hypertension, cigarette smoking, female sex, age and positive family history should be considered in the assessment of treatment of un-ruptured intracranial aneurysms.

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Bangladesh Journal of Neuroscience 2019; Vol. 35 (2): 95-103

Study of Rare Cases of Congenital Myasthenic Syndrome in Bangladesh

BANU A[1], RAHMAN MM[2], ANWAR MM[3], AHMED R[4], AZAD MAK[5], KABIR J[6], AHMED A[7], SARKAR D[8], JAHAN SMS[9],OHAB MA[10], ALAM MS[11], HAQUE MA[12], SHAHEDUZZAMAN AKM[13], RAHMAN MM[14], MONDOL SI[15], SARKAR MK[16], MIAH MH[17],MONDOL R[18], RABBANI MG[19], PONDIT PK[20], SARKAR NC[21], SARKAR MRA [22], AZAD AK[23], ADILUZZAMAN MAFA[24], KARMOKAR P[25], SUTRADHAR P[26], MAMOON MA[27], MONDOL F[28], SHAFIUJJAMAN ASM[29],

Abstract:

Congenital myasthenic syndromes (CMS) comprise a heterogeneous group of rare inherited diseases in which the neuromuscular transmission in the motor plate is compromised by one or more genetic pathophysiological specific mechanisms are characterized by fatigable weakness of skeletal muscle (e.g., ocular, bulbar, limb muscles) with onset at or shortly after birth or in early childhood; rarely, symptoms may not manifest until later in childhood. The diagnosis of CMS is based on clinical findings, a decremental EMG response of the compound muscle action potential (CMAP) on low-frequency (2-3 Hz) stimulation, absence of anti-acetylcholine receptor (AChR) and anti-MuSK antibodies in the serum, a positive response to acetylcholinesterase (AchE) inhibitors and lack of improvement of clinical symptoms with immunosuppressive therapy. Pathogenic variants in one of multiple genes encoding proteins expressed at the neuromuscular junction are currently known to be associated with subtypes of CMS. The most commonly associated genes include: CHAT, CHRNE, COLQ, DOK7, GFPT1 and RAPSN. We studied on a sibling presented with progressive fatigability and fluctuating ptosis with frequent exacerbations of muscle weakness during infections since infancy. On both cases CT scan of chest were negative for thymoma, antibodies

1. Dr. Akter Banu, Assistant Professor, Department Of Pediatrics, Rangpur Medical College, Rangpur.
2. Dr. Md. Mahfuzer Rahman, Professor, Department Of Medicine, Rangpur Medical College, Rangpur.
3. Dr. Md Mahfuj Ul Anwar, Assistant Professor, Department Of Medicine, Rangpur Medical College, Rangpur.
4. Dr. Raihan Ahmed, Indoor Medical Officer, Department of Medicine, Rangpur Medical College Hospital, Rangpur.
5. Dr. Md. Abul Kalam Azad, Assistant Professor, Department of Medicine, Rangpur Medical College, Rangpur.
6. Dr. Jahangir Kabir, Assistant Professor, Department of Medicine, Rangpur Medical College, Rangpur.
7. Dr. Anis Ahmed, Assistant Professor, Department of Neurology, BSMMU, Dhaka.
8. Dr. Devendranath Sarkar, Professor, Department of Medicine, Rangpur Medical College, Rangpur.
9. Dr. Shah Md. Sarwer Jahan, Professor, Department of Medicine, Rangpur Medical College, Rangpur.
10. Dr. MA Ohab, Associate Professor, Department of Medicine, Rangpur Medical College, Rangpur.
11. Dr. Shafiul Alam, Associate Professor, Department of Medicine, Rangpur Medical College, Rangpur.
12. Dr. Md. Ashraful Haque, Associate Professor, Department of Medicine, Rangpur Medical College, Rangpur.
13. Dr. AKM Shaheduzzaman, Associate Professor, Department of Medicine, Rangpur Medical College, Rangpur.
14. Dr. Md. Mokhlesur Rahman, Associate Professor, Department of Medicine, Rangpur Medical College, Rangpur.
15. Dr Shariful Islam Mondol, Associate Professor, Department of Medicine, Rangpur Medical College, Rangpur.
16. Dr. Md. Kamruzzaman Sarkar, Associate Professor, Department of Medicine, Rangpur Medical College, Rangpur.
17. Dr. Md. Helal Miah, Assistant Professor, Department of Medicine, Rangpur Medical College, Rangpur.
18. Dr. Rahenur Mondol, Assistant Professor, Department of Medicine, Rangpur Medical College, Rangpur.
19. Dr. Md. Golam Rabbani, Assistant Professor, Department of Medicine, Rangpur Medical College, Rangpur.
20. Dr. Prosanto Kumar Pondit, Assistant Professor, Department of Neurology, Rangpur Medical College, Rangpur.
21. Dr. Narayan Chandro Sarkar, Assistant Professor, Department of Medicine, Rangpur Medical College, Rangpur.
22. Dr. Md. Ruhul Amin Sarkar, Assistant Professor, Department of Medicine, Rangpur Medical College, Rangpur.
23. Dr. Abul Kalam Azad Assistant Professor, Department of Medicine, Rangpur Medical College, Rangpur.
24. Dr. Md. Al Fatah Al Adiluzzaman, Assistant Professor, Department of Medicine, Rangpur Medical College, Rangpur.
25. Dr. Priobrata Karmakar, Assistant Professor, Department of Medicine, Rangpur Medical College, Rangpur.
26. Dr. Probal Sutradhar, Specialist (Medicine), Haragach 31 Beded Hospital,Rangpur.
27. Dr. Md. Abdullah Al Mamoon, Indoor Medical Officer, Department of Medicine, Rangpur Medical College Hospital, Rangpur.
28. Dr. Firoz Mondol, Registrar, Resident, Internal Medicine, Rangpur Medical College, Rangpur
29. Dr. ASM Shafiujjaman, Registrar, Medicine, Rangpur Medical College, Rangpur.

against the acetylcholine receptor (AChR) and the muscle specific kinase (MuSK) were negative and decremental response on electrophysiological study of Repetitive nerve stimulation (RNS) and EMG were consistent with disease of neuromuscular junction (post synaptic) and they were only on pyridostigmine for long time with marked improvement of symptoms and signs. Considering all scenario both of our cases mostly fits with the autosomal recessive, post synaptic CMS associated with Rapsyn deficiency.

Objective : *As in Bangladesh, there is inadequate data on the epidemiological profile of CMS, our aim is to describe these cases for their rarity and the difficulty encountered in diagnosis as they are easily confused with Juvenile Myasthenia Gravis (JMG) and familial myopathies. As both the cases are very rare, it should be an original article.*

Key word: *Progressive fatigability, Repetitive Nerve stimulation, Auto-antibodies, Congenital Myasthenic Syndrome.*

Introduction:

Congenital myasthenic syndromes (CMS) are a heterogeneous group of early-onset genetic neuromuscular transmission disorders due to mutations in proteins involved in the organisation, maintenance, function, or modification of the motor endplate. CMS are clinically characterised by abnormal fatigability, or transient or permanent weakness of extra-ocular, facial, bulbar, truncal, respiratory or limb muscles[1]. Congenital myasthenic syndromes can be classified according to the pattern of inheritance, based on the altered protein involved in the motor plate, or by taking into account the site at the neuromuscular junction (pre-synaptic, synaptic, or postsynaptic) involved with the dysfunction[2].

The age of onset, severity of presenting symptoms, and distribution of muscle weakness can vary from one patient to another. Congenital myasthenic syndromes (CMS) are characterized by fatigable weakness of skeletal muscle (e.g., ocular, bulbar, limb muscles) with onset at or shortly after birth or in early childhood; rarely, symptoms may not manifest until later in childhood. Severity and course of disease are highly variable, ranging from minor symptoms to progressive disabling weakness[3]. In some subtypes of CMS, myasthenic symptoms may be mild, but sudden severe exacerbations of weakness or even sudden episodes of respiratory insufficiency may be precipitated by fever, infections, or excitement. Cardiac and smooth muscle are usually not involved. Coordination, sensation, and tendon reflexes are normal; cognitive skills are usually normal. A variety of additional symptoms affecting other organ systems can be present in specific subtypes. Some myasthenic symptoms are present at birth. Respiratory insufficiency with sudden apnea and cyanosis are common findings in neonates. Neonates with CMS can have multiple joint contractures (often described as arthrogryposis multiplex congenita [AMC]) resulting from a lack of fetal movement in utero. Other major findings in the neonatal period may include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and facial, bulbar, and generalized weakness. Stridor in infancy may be an important clue to CMS. Individuals with onset later in childhood show abnormal muscle fatigability, with difficulty in running or climbing stairs. Motor milestones may be delayed. Affected individuals present with fluctuating eyelid ptosis and fixed or fluctuating extraocular muscle weakness. Ptosis may involve one or both eyelids. In addition, facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing may be present. Spinal deformity or muscle atrophy may occur [4]. Most CMS are transmitted by autosomal recessive inheritance [3].

A generic diagnosis of a CMS can be made on clinical grounds from a history of fatigable weakness involving ocular muscles, bulbar muscles (muscles of the face, and muscles used for speaking and swallowing), and limb muscles since infancy or early childhood, a history of similarly affected siblings, and a variety of tests. Such tests include a decremental response on Repetitive Nerve stimulation (RNS) and Electromyography (EMG), and negative tests for antibodies against the acetylcholine receptor

(AChR) and the muscle specific kinase (MuSK). Genetic diagnosis of the CMS is important because therapy that benefits one type CMS may worsen another type[3].

The prevalence of CMS is very difficult to estimate due to the clinical variability of cases and the fact that many cases have no specific etiologic diagnosis or are undiagnosed. Since they are rare medical conditions in which definite diagnosis rests on clinical, electromyography and specific genetic testing, few data are available. Furthermore, there are few series of patients where this complete diagnostic profile has been established, and most of the current knowledge has been obtained by reports of isolated case reports[5]. According to a recent review, the prevalence of CMS is estimated as 1/10 that of myasthenia gravis, which is 25–125/1000000[6]. A study in the UK estimated that the prevalence of CMS with a defined genetic diagnosis is approximately 9.2 cases per million children under 18 years old in the population[7]. An important epidemiological profile on CMS was obtained in a study performed at the Mayo Clinic. Most cases occurred as a consequence of postsynaptic defects (68%), and basal lamina defects (13.7%), development and maintenance of the end plate defects (12.5%), pure presynaptic defects (5.9-8%) and congenital myopathies with secondary neuromuscular junction transmission defects (0.3%) also represent other rare congenital myasthenic syndromes. Thus, postsynaptic forms represent up to 75-80% of all CMS cases[5,8,9]. In Western or central Europe the RAPSN variant c.264C>A and the DOK7 variant c.1124_1172dupTGCC are highly prevalent [10]. In a study of 34 CMS families from Israel the genes most frequently mutated were RAPSN (n=13), COLQ (n=11), and CHRNE (n=7)[11]. All other mutated proteins may contribute with less than 1% of the CMS cases to the general group of CMS. About 75% of the CMS cases are due to mutations in genes that encode different subunits of the acetylcholine receptor (CHRNA1, CHRNB1, CHRND, CHRNE) or proteins important to maintain the structure or function of the NMJ, such as MUSK, RAPSN or DOK7 [12,13]. The most common causative genes are CHAT, COLQ, RAPSN, CHRNE, DOK7, and GFPT1[1].

The clinical picture of congenital myasthenic syndromes (CMS) is similar to that of myasthenia gravis (MG), in which individuals have a history of fatigable weakness involving ocular, bulbar, and limb muscles; however, the myasthenic symptoms of CMS usually start at or shortly after birth rather than in adulthood, as is usual for MG. Because seronegative autoimmune MG has been reported on occasion in children younger than age two years, MG may be difficult to differentiate from CMS, especially in later childhood or adulthood. Furthermore, immunosuppressive therapy does not improve clinical symptoms in CMS, whereas it does in MG. Other disorders partially resembling CMS at childhood to consider are Spinal muscular atrophy, Congenital muscular dystrophies, Congenital myopathies including X-linked myotubular myopathy nemaline myopathy and multiminicore myopathy, Infantile myotonic dystrophy type 1,Mitochondrial myopathies, Brain stem anomalies, Mobius syndrome, Infantile botulism [4].

To establish the extent of disease and needs in an individual diagnosed with congenital myasthenic syndromes (CMS), the following evaluations are recommended: Assessment of strength and motor function; in children, assessment of motor, speech, and cognitive development. Assessment of respiratory function with baseline pulmonary function tests including forced vital capacity in sitting and supine positions and blood gas exchange. Polysomnography to identify individuals with nocturnal hypoventilation.Assessment of contractures and joint deformities by physiatrists and orthopedists; radiologic examinations if spinal deformity is observed. Speech therapy evaluation if dysarthria and/or hypernasal speech is present. For early-onset forms, assessment of feeding abilities (sucking, swallowing, gastroesophageal reflux)and growth parameters to determine the need for feeding interventions such as gavage feeding or gastrostomy insertion[4].

There are no recent published consensus guidelines for the management of CMS treatment. The choice of medical treatment varies with the

CMS subtype. Therefore, it seems reasonable to consider a first-linegenetic test to evaluate the genetic subtype. Most individuals with CMS benefit from Acetylcholineesterase (AChE) inhibitors (pyridostigmine) and/or the potassium channel blocker 3,4-diaminopyridine (3,4-DAP); however, caution must be used in giving 3,4-DAP to young children and individuals with fast-channel CMS (FCCMS). Individuals with *COLQ* and *DOK7* pathogenic variants usually do not respond to long-term treatment with AChE inhibitors. Some individuals with slow-channel CMS (SCCMS) are treated with quinidine, which has some major side effects and may be detrimental in individuals with AChR deficiency. Fluoxetine is reported to be beneficial for SCCMS. Ephedrine and albuterol have been beneficial in several individuals, especially as a therapeutic option for those with *DOK7* or *COLQ* pathogenic variants. In addition to medical therapy, a multidisciplinary approach to the clinical management of the affected individual greatly improves quality of life and can influence survival. Management should be tailored to each individual, their specific CMS subtype, and rate of progression. Depending on the individual clinical situation the clinical management may include the Physical and occupational therapy, speech therapy, orthotics or a wheelchair, a percutaneous gastric tube, ventilator support and genetic counseling [4]

Case presentation:

A 14 years old boy (case 1) from Bangladesh, born of consanguineous parents presented with progressive fatigability and fluctuating ptosis, more marked after exercise. The illness started at the age of 1.5 years. Initially his parents noticed delayed motor developmental milestones such as sitting, walking, feeding difficulties and then ptosis added. He suffered frequent episodes of respiratory tract infections since infancy with exacerbation of muscle weakness during infections. At the age of 9 years, he was diagnosed as a case of Congenital Myasthenic Syndrome (CMS) on the basis of history and clinical examinations and prescribed with pyridostigmine and noticed marked improvement of symptoms with reappearance of symptoms on stopping of medication but he did not get any immunosuppressive therapy including corticosteroid, plasma exchange or thymectomy. Clinical examination of the boy revealed normal intellectual function, nasal voice, elongated face, high arched palate, bilateral partial ptosis, generalized muscle wasting, hypotonia, intact superficial and deep reflexes, waddling gait, kyphosis, hyperlordosis, laxed skin, no external ophthalmoplegia.

His younger sister (case 2), who was 5 years old also presented with progressive fatigability more marked after exercise and delayed motor developmental milestones such as sitting, walking, feeding difficulties and then ptosis since the age of 3 years. None of their other family members suffered from similar illness. She had also been on pyridostigmine for 2 year with marked improvement of symptoms and signs. Clinical examination of the girl revealed normal intellectual function, nasal voice, high arched palate, bilateral partial ptosis, generalized muscle wasting, hypotonia, intact reflexes, waddling gait, laxed skin, no external ophthalmoplegia.

Bed sided tests (Cogan's lid twitch sign, curtain sign, ice on eye test, tensilon test) were positive for myasthenia in both patients.

On investigations similar findings were recorded on both cases. Routine blood examinations were normal. Liver function test, renal function test, creatine kinase (CK) were normal. ECG, Echocardiogram were within normal limit. CT scan of chest was negative for thymoma. Antibodies against the acetylcholine receptor (AChR) and the muscle specific kinase (MuSK) were negative and decremental response on electrophysiological study of Repetitive nerve stimulation (RNS) and EMG were consistent with disease of neuromuscular junction (post synaptic).

Discussion:

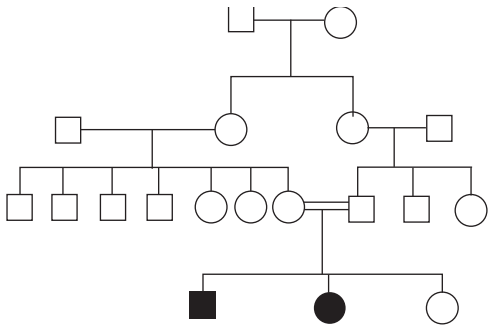
At present there are no well-defined diagnostic criteria for CMS. Congenital myasthenic syndromes should be suspected in cases of: (i) early-onset fatigable muscle weakness mainly involving ocular, bulbar and proximal limb musculature (generally varying from birth to late childhood); (ii) a positive family history of a specific disorder or sometimes only the history of a

hypotonic infant; (iii) clinical and neurophysiological myasthenic findings with a negative antibody testing profile; (iv) electromyography (EMG) studies showing decremental responses of 10% or more in the amplitude or in the quarter of the area from the first evoked compound motor action potential (CMAP), or single-fiber EMG studies compatible with a neuromuscular junction dysfunction; and (v) the presence of a specific clinical syndromic phenotype (i.e. Escobar syndrome, Pierson syndrome) [9,14,15]. Both of our cases fulfilled most of the above mentioned criteria.

Although cases of myasthenia gravis during infancy and childhood such as Juvenile Myasthenia Gravis (JMG) have been described in the literature since 1960,[16-18] the distinction between acquired autoimmune form and congenital forms has been increasingly recognized and emphasized [19-28]. This increasing awareness regarding congenital forms of myasthenia gravis was originally described in a previous study described the nosology of congenital myasthenic syndrome [29]. The current thrust of research is naturally directed towards elucidation of molecular basis of such disorders [30-35]. Two major features distinguish CMS from acquired autoimmune myasthenia gravis (MG) are a positive family history and absence of AChR antibodies. In this study both patients are siblings having absence of Anti-AchR and Anti-MuSK antibodies. While a positive family history is consistent with the diagnosis of CMS, a negative family history does not exclude autosomal recessive inheritance, an incompletely penetrant autosomal dominant gene in one parent, or a new mutation [36]. Furthermore, while most cases of acquired autoimmune childhood MG are sporadic, familial aggregates have been observed which may be due to inheritance of HLA haplotypes that predispose to sensitisation of acetylcholine receptor (AChR) [36]. On the other hand, while a positive AChR antibody test excludes the diagnosis of CMS, but a negative test in a sporadic case does not necessarily imply a diagnosis of CMS because a high proportion of juvenile patients with autoimmune MG are also seronegative [37]. It is important to note here that correct differentiation of CMS from autoimmune MG is also important therapeutically, as CMS patients do not respond to immunosuppressive therapy or plasma exchange and thymectomy [38]. Treatment of JMG commonly includes anticholinesterases, corticosteroids and newer immune modulating agents, plasma exchange and intravenous immunoglobulin (IVIG) and thymectomy [39]. Acetylcholinesterase inhibitor is the first line therapy may be sufficient in ocular JMG or mild generalised JMG [40]. Frequently some form of immunosuppression or immunomodulation is required to improve symptoms of JMG. Corticosteroids are often effective and sometimes are the mainstay of therapy[41]. A systematic review of the literature concluded that thymectomy increases the probability of remission or improvement of symptoms in AChR seropositive, nonthymomatous, autoimmune MG[42].In our study both of the patients were on pyridostigmine for long time noticing marked improvement of symptoms with reappearance of symptoms on stoppage of drug. And neither of the patients needed any immunosuppressive therapy, plasma exchange or thymectomy. Such scenario goes in favor of CMS rather than Autoimmune MG.

A temporary form of MG affects 10% to 20% of newborns whose mothers have immune-mediated MG known as Transient Neonatal Myasthenia Gravis (TNMG) [43]. Our cases did not have any history of maternal MG.

Most CMS are transmitted by autosomal recessive inheritance [3]. CMS due to mutations within the *RAPSN* gene is an autosomal recessive (AR) disorder [44]. The consanguinity of parents, unaffected parents of our cases are suggestive of AR inheritance.



On EMG or RNS studies, CMS show decremental response of 10% or more in the amplitude or in the quarter of the area from the first evoked compound motor action potential (CMAP), or single-fiber EMG studies compatible with a neuromuscular junction dysfunction [8,14,15]. Postsynaptic forms represent up to 75-80% of all CMS cases [5,8,9]. Both of our patients' decremental response on electrophysiological study of RNS and EMG were consistent with disease of neuromuscular junction (post synaptic).

Postsynaptic CMS are subdivided into Primary AChR deficiency, Kinetic abnormalities of the AChR (such as Fast Channel CMS & slow channel CMS) and defects within the AChR clustering pathway (specially CMS associated with deficiency of Rapsyn and Plectin) [1,45]. Slow channel CMS is an autosomal disorder and deterioarates with AChR inhibitors [38]. CMS associated with deficiency of Plectin is refractory to pyridostigmine [2]. On the other hand, primary AChR deficiency, fast channel syndrome, Rapsyn deficiency are well responsive to pyridostigmine. Fast channel CMS (FCCMS) usually present in early childhood with infantile phenotype 46. FCCMS arises from autosomal recessive mutations in different domains of the acetylcholine receptor subunits and clinically mimicks a typical autoimmune acquired myasthenia gravis starting in the first decade of life with good clinical response to treatment with pyridostigmine and amiframpidine [2]. Primary deficiency of the acetylcholine receptor results from mutations in genes coding any of the subunits of the acetylcholine receptor, with those related to the μ subunit being the most severe [5,15]. The clinical picture is characterized by ptosis, refractory marked ophthalmoparesis and severe muscle weakness of the limbs. There is generally a partially responsive pattern to pyridostigmine, amifampridine and albuterol use in clinical practice [5,15,17]. A very good response to pyridostigmine virtually rules out end plate Ach deficiency [38]. Our cases responded well with AChE inhibitors with history of reappearance of symptoms on stoppage of medication without adding any immunosuppressive therapy, plasma exchange or thymectomy.

Rapsyn concentrates and anchors the acetylcholine receptor in the postsynaptic membrane and is needed for the development of the junctional folds [48]. Most patients with rapsyn deficiency present in the first year of life, with a few presenting in childhood or adult life [49]. Both of our cases presented at 2nd year of age. Rapsyn mutations produce a CMS in which respiratory distress, hypotonia, and poor feeding are usually present at birth. There is generalized weakness and ptosis but ophthalmoplegia is uncommon. Patients have a high-arched palate and may have arthrogryposis [43]. Infections can precipitate exacerbation of clinical manifestations [50]. In few patients prominent hyperlordosis can occur [51]. In our cases, there was hypotonia (more in case 1), generalized weakness and ptosis (both case), high-arched palate & hyperlordrosis (case 1) and history of exacerbation of symptoms during RTI.

Conclusion

Among the postsynaptic CMS, Rapsyn deficiency is most common and widely studied. Without genetic analysis it is not possible to differentiate among the different varieties of post synaptic CMS precisely but considering the all clinical and investigations scenario both of our cases mostly fits with the autosomal recessive, post synaptic CMS associated with Rapsyn deficiency.

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Bangladesh Journal of Neuroscience 2019; Vol. 35 (2): 104-109

REVIEW ARTICLE

Understanding Hemifacial spasm: A Review Of An Uncommon Movement Disorder

ANWAR N[1], NAHAR S[2], ANWAR NB[3] , ULLAH AKM A[4]

Abstract:

Hemifacial Spasm is a rare condition and often misdiagnosed even by neurologists. Although etiology, pathophysiology is clear, treatment is unsuccessful in many cases. In this review article we focus on etiology, pathophysiology, diagnosis and management of this infrequent movement disorder.

Keywords: *Hemifacial Spasm, Movement Disorder.*

Introduction:

Hemifacial spasm (HFS) is characterized by unilateral, paroxysmal, involuntary movement occurring in the muscles innervated by the ipsilateral facial nerve. The involuntary contractions usually begin in the orbicularis oculi muscle and gradually spread to the other muscles related to facial expression[1]. The majority of HFS cases occur unilaterally with an estimated 0.6% to 5% occurring bilaterally[2]. Some patients report worsening of spasms with fatigue, anxiety, and changes in position of the head (e.g., head to one side or the other on the pillow at night)[3].

Although traditionally perceived as a benign illness, it can lead to increasing embarrassment and social withdrawal for the individual and in severe cases even functional blindness due to involuntary eye closure.

Historical Perspective

F Schultze, in 1875, probably reported the first case of hemifacial spasm in literature, when he described a 56-year-old man with involuntary movements involving the left side of his face. The post-mortem revealed a giant aneurysm of the left vertebral artery compressing the left facial nerve[4].

In 1888, Gowers elaborated on this syndrome further and described the classical features of this condition[5].

The condition received its current terminology, when it was named as 'he´mispasme facial' by Babinski in 1905. Babinski at the same time also described another characteristic feature of this disease, thereafter known as 'the other Babinski sign' i.e. when orbicularis oculi contracts and the eye closes, the internal part of the frontalis contracts at the same time, and the eyebrow rises during eye occlusion.''[6]. This typical feature distinguishes hemifacial spasm from blepharospasm in which this sign is absent.

Epidemiology

HFS is prevalent in 9.8 per 100,000 persons[7]. The average age of onset for HFS is 44 years. Women and Asian populations have an increased susceptibility to HFS though valid prevalence data is scarce[8,9,10]. Worldwide estimates for the prevalence of HFS are 14.5 per 100,000 women and 7.4 per 100,000 men[11,12]. Families with HFS present with autosomal dominant inheritance and low penetrance although there have been only a few reported cases[13]. In addition, the genetic susceptibility is poorly defined as there is not a clear relationship between HFS and single-nucleotide polymorphisms in genes related to vascular compression[14].

1. Dr. Nayeem Anwar, Assistant Professor, Department of Neurology, Bangabandhu Shiekh Mujib Medical University(BSMMU), Shahbag, Dhaka.
2. Prof. Shamsun Nahar, Professor, Dept. of Physical Medicine and Rehabilitation, BSMMU, Shahbag, Dhaka.
3. Dr. Nawreen Binte Anwar, FCPS (Ophthalmology) Final part student, Bangladesh College of Physicians and Surgeons (BCPS), Mohakhali, Dhaka.
4. Dr. AKM Anwar Ullah, Ex-Professor, Dept. of Neurology, BSMMU, Shahbag, Dhaka.

Pathophysiology

The accepted underlying pathophysiology of HFS suggests that the disease process is caused by facial nerve root entry zone myelin breakdown and ephaptic transmission, which is the passage of neural impulses through artificial chemical or chemical synapses. The root exit zone of the facial nerve is defined as the transition point between central (oligodendrocytes) and peripheral (Schwann) cell myelination[15,16]. This segment is sheathed by only an arachnoidal membrane and lacks both interfascicular connective tissue separating fibers and epineurium; these features increase this segment's vulnerability to compression[16]. Compared to similar disorders of the trigeminal, glossopharyngeal, and vagus nerves, a study correlated the length and volume of central myelin portions of these nerves with the incidence of the nerves' corresponding diseases [17]. One study suggested that the root exit zone was primarily involved in only 23% of its studied HFS patients whereas compression of a more proximal segment of the facial nerve when it emerges from the pontomedullary sulcus was implicated in 73%[18].

Several theories have been put forward to explain how this compression of the facial nerve at its root exit/entry zone leads to hemifacial spasm.

One of them – the nerve origin hypothesis or the peripheral theory postulates that there is emphatic transmission of impulses between neighbouring neurons(i.e. coupling of adjacent nerve fibers due to local exchange of ions or local electric fields) leading to excessive or abnormal firing. Myelination is a natural inhibitor of ephaptic transmission and the demyelination due to local compression thus leads to hemifacial spasm[19].

The other – the nuclear origin hypothesis or the central theory states that hemifacial spasm results from the hyperexcitability of the facial motor nucleus due to irritative feedback from peripheral lesions of the nerve[20].

Etiology

Hemifacial Spasm can either be primary or secondary. Primary HFS results from compression of the seventh nerve at the root exit zone in the posterior cranial fossa by an aberrant or ectatic vessel, most commonly the superior cerebellar, the anterior inferior cerebellar or the vertebral artery[21]. The pattern of neurovascular compression can be divided into six different categories: (A) loop type, where the vascular loop itself creates the compression, (B) arachnoid type, where arachnoid trabeculae between the vessel and brainstem cause the vessel to tether to the nerve, (C) perforator type, where the perforating arteries from the compressing vessel tether the vessel to the brainstem, (D) branch type, where the nerve is caught between the compressing vessel and its branches, (E) sandwich type, where the nerve is sandwiched between two different vessels, and (F) tandem type, where one vessel compresses another vessel that compresses the nerve[22].

Secondary HFS occurs with damage anywhere along the facial nerve from the internal auditory canal to the stylomastoid foramen[23]. Cases of secondary HFS have been linked to cerebellopontine angle (CPA) tumors and vascular malformations with other case linked to facial nerve trauma, demyelinating lesions, and vascular insults[24]. Collectively, these underlying issues of secondary HFS are thought to cause neural dysfunction and/or irritation of the facial nerve pathway[25].

Diagnosis

Diagnosis of hemifacial spasm is mainly a clinical one. All patients must be subjected to a detailed history and clinical examination to look for any subtle neurological deficits which would point to an underlying secondary cause for the condition. The "Babinski-2 sign," "other Babinski sign," or "brow-lift sign" is a physical exam maneuver that is positive when a patient lifts his/her eyebrow with ipsilateral eye closure, signaling the synchronized activity of the frontalis and orbicularis oculi muscle during HFS[26,27,28]. This technique has been shown in one study to have high sensitivity (86%), specificity (100%), and interrater reliability (92%) for HFS diagnosis[29].

Electromyography (EMG), Magnatic Resonance Image (MRI), and computerized tomography (CT) are used to confirm the diagnosis and differentiate

primary from secondary HFS. EMG can also be useful to differentiate HFS from other abnormal facial movement disorders; in HFS, spontaneous, high-frequency synchronized firing is seen on EMG [30]. Additional diagnostic techniques such as a CT angiogram are useful for microsurgical planning[31].

Treatment

Hemifacial spasm is a chronic condition with progressively increasing spasms. However due to the low prevalence of the condition, not a lot of controlled clinical trials have been done to determine the best therapeutic modality for these patients. Although, botulinum toxin remains the most popular choice for therapy, other options including oral pharmacotherapy and microsurgical decompressive surgeries are also beneficial in selected cases.

Drugs

A large number of drugs have been studied and found to be of some efficacy in hemifacial spasm. These include anticonvulsants such as carbamazepine, clonazepam, gabapentin and other drugs like baclofen, anticholinergics and haloperidol[32]. The biggest limitation of oral drugs is their inconsistent efficacy and large number of side effects including sedation, fatigue and exhaustion[33].

Botulinum toxin therapy

The standard medical treatment for HFS is botulinum neurotoxin (BoNT) injections. Having been used since the early 1980s, BoNT injections provide low-risk symptomatic relief in 85% of HFS patients, making it the treatment of choice for patients with high anesthetic risk and those who refuse surgery[34].

Botulinum toxin is a potent biological toxin derived from the organism Clostridium botulinum(35). It acts on the presynaptic region of the neuromuscular junction and prevents the calcium-mediated release of acetylcholine at the nerve terminal preventing impulse generation downstream resulting in functional reversible paralysis of the supplied muscles. Based on target site of action there are various serotypes of Botulinum Toxin. The most commonly used commercially available preparation is type A. The resulting muscular weakness due to the injected toxin lasts for somewhere between 3-6 months. A large number of trials have validated the successful outcomes of this therapy with improvements in as many as 75-100% of individuals with hemifacial spasm[36,37]. However, the injections must be repeated every 3 to 6 months. Tolerance can develop in some cases, but the treatment is generally well tolerated. Local complications of these injections include ptosis, blurred vision, and diplopia that may improve after days to weeks[38].

Surgery

With the advent of botulinum toxin therapy, the need for operative intervention has drastically gone down in cases of hemifacial spasm.

Microvascular decompression (MVD) provides a curative treatment with long term relief of symptoms by alleviating vascular compression of the facial nerve root. The underlying principle of MVD is to separate the nerve-vessel conflict rather than isolate it with prostheses; important intraoperative considerations include prompt identification of the neurovascular conflict site, sharp dissection of arachnoids for maximal nerve root visualization, and electrophysiological monitoring to distinguish offending vessels[39]. MVD has excellent results with long-term success rates between 83% and 97% of cases[40].

An analysis of twenty-two papers representing 5,685 patients treated with MVD for HFS found that an average of 91.1% of patients had complete resolution of symptoms over a median 2.9-year follow-up period[41]. Even with a first-time MVD failure, patients in one study who elected for repeated MVDs had a cure rate of 85% and did not suffer a higher rate of complication with a mean follow-up of 54.48 months[42]. Another small study found no significant difference between elderly and young patients in cure rate (96.3% versus 89.4%) and complication rate[43].

Resolution of HSF after MVD may take several months to several years with small percentage of patients who fail to improve. In these patients, failure to improve may be attributed to inadequate decompression of the offending vessel, presence

of a previously unidentified secondary offending vessel, or implant compression/migration against the facial nerve (44). Generally, complications of MVD are uncommon and generally transient (45). In some cases, MVD can result in serious complications, which are thought to be caused by facial nerve stretching during cerebellar retraction, iatrogenic injury to surrounding structures, or prosthesis compression (46). Overall, serious complications following MVD were reported in less than 1% of cases(47).

Conclusion

The benign appearing facial twitches of hemifacial spasm are actually very bothersome to the individuals who suffer from the condition both in terms of functional blindness as well as social embarrassment. Early recognition of the condition, ruling out secondary causes and instituting appropriate therapy is therefore a necessity. Botulinum toxin therapy offers a simple, noninvasive therapy for this condition. Patients who do not respond to the toxin injections or prefer a permanent cure can be offered surgical options as well. Either treatment modality when instituted gives good benefits to the patient and leads to a significant improvement in their quality of life.

Acknowledgments and Disclosure Statements

The authors report no conflicts of interest related to this study.

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Bangladesh Journal of Neuroscience 2019; Vol. 35 (2): 110-114

CASE REPORT

A Case Report of Reverse Split-hand Syndrome: An Overlooked Clinical Sign of Hirayama Disease

SAHA S[1], RAHMAN HZ[2], ISLAM MR[3], ALAM SK[4], MUZAHID MAA[5], CHOWDHURY A[6], HASAN M[7], ROY U[8], KABIR MS[9]

Abstract:

Hirayama disease (HD) is considered to be a relatively benign, slowly progressive and less disabling rare neurological disorder where flexion induced compressive ischemic lower cervical myelopathy causes selective anterior horn cell injury resulting weakness and atrophy of distal upper limb without any pyramidal, spinothalamic and posterior column disturbance. Herein, we report a young male with clinical and imaging features suggestive of Hirayama disease presented with dissociated hand muscle atrophy (hypothenar more affected than thenar) in both hands. This less recognized finding was previously termed as reverse split-hand syndrome just opposite to split-hand syndrome found in amyotrophic lateral sclerosis. We also observe electrophysiological correlation of reverse split-hand syndrome in HD.

Key words: *Reverse split-hand syndrome, Hirayama disease, split-hand syndrome, Amyotrophic lateral sclerosis*

Introduction:

Hirayama disease (HD) is a rare neurological disorder where either unilateral or bilateral wasting & weakness of forearm and hand muscles occur. In 1959 Hirayama et al. first described the condition as 'Juvenile muscular atrophy of unilateral upper extremity'[1, 2].Other names used to describe this process are benign juvenile brachial spinal muscular atrophy, juvenile asymmetric segmental spinal muscular atrophy, juvenile muscular atrophy of the distal upper extremity, monomelic amyotrophy and oblique amyotrophy[3]. Recently the term brachial amyotrophy spectrum included classical form-unilateral distal involvement or brachial monomelic amyotrophy (BMMA)[1,2,4,5], distal asymmetric amyotrophy[5,6], distal bimelic amyotrophy (DBMA)[7,8], bilateral proximal or proximo-distal forms[9]. It is relatively benign, young age at onset, slowly progressive usually not more than five years and can be disabling sometimes. But disability can be reduced to a great extent if early intervention can be applied. Male are affected more than female (3:1) with high prevalence in Asia particularly in Japan but also noted in China, Taiwan, Malaysia, India, and Sri Lanka, with few cases from Europe and North America. The condition is assumed to be caused by chronic ischemic changes to the anterior horn cells of the cervical cord, caused by limited dural sac laxity& altered cervical spine dynamics[3]. Sensory functions, reflexes & bowel-bladder remain normal and lower extrimities are also not involved here. However a characteristic pattern of wasting was observed in HD where hypothenar muscles

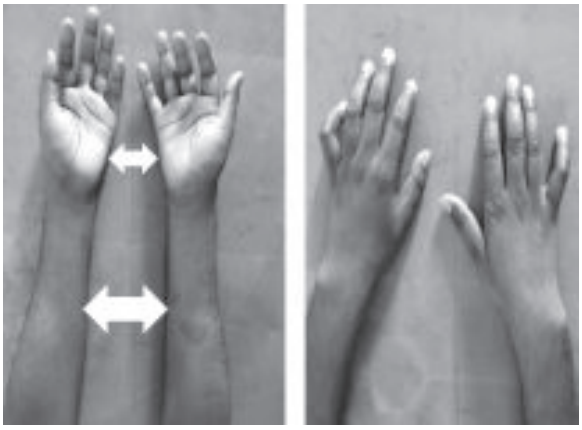
1. Sujan Saha, Phase B Resident, Dept. of Neurology, BSMMU
2. Hasan Zahidur Rahman, Professor, Dept. of Neurology, BSMMU
3. Md. Rafiqul Islam, Professor And Chairman, Dept. of Neurology, BSMMU
4. SK. Mahbub Alam, Assocate Professor, Dept. of Neurology, BSMMU
5. Md. Abdullah Al Muzahid, Phase B Resident, Dept. of Neurology, BSMMU
6. Ashish Chowdhury, Phase B Resident, Dept. of Neurology, BSMMU
7. Mehedi Hasan, Phase B Resident, Dept. of Neurology, BSMMU
8. Uttam Roy, Phase B Resident, Dept. of Neurology, BSMMU
9. Md. Suman Kabir, Phase B Resident, Dept. of Neurology, BSMMU

(abductor digiti minimi-ADM) were more affected with relative preservation of thenar muscle (abductor polocis brevis-APB). This phenomenon is just opposite to split hand syndrome characteristically found in amyotrophic lateral sclerosis (ALS) where thenar muscles (APB) are more wasted than hypothenar muscles (ADM). So the term reverse split hand has been introduced[10]. In this case report we observed electrophysiological correlation with reverse split hand syndrome in HD.

Case report:

A 23-year-old right handed Bangladeshi male of non-consanguineous parents presented with insidious onset slowly progressive weakness and wasting of both upper limbs for about 3 years. His right upper limb was affected first and one year later left upper limb was also involved. Weakness and wasting were more marked distally. At first he noticed mild clumsiness in right hand and occasional slippage of objects from hand. But he had no difficulty in raising the arm above head or flex the forearm. He developed gradual wasting of medial aspect of hand and then forearm without any muscle twitching. One year later his left upper limb was also involved in same manner. He also noticed tremulous movement of right hand on stretching and could not straighten the fingers properly. He could hold a pen or key and grip an object with a feeling of heaviness. He was performing his daily activities with little modification. There was no tingling, numbness or paresthesia in the limbs. His lower limbs were normal without any weakness, wasting, sensory complaints or walking difficulty. His bowel and bladder habits were normal. He had no history of neck pain or trauma to the neck as well as exposure to toxin. Patient did not complaint of difficulty in deglutition, headache, visual disturbance, convulsion or learning difficulty. His milestones of development were normal and family history was also noncontributory.

On examination we found gross wasting of hypothenar muscles of hand and medial aspect of forearm in both upper limbs (right>left) without any fasciculation but there was tremor in outstretched hands. Lateral aspect of hand and forearm were remarkably preserved denoting reverse split-hand (Figure 1A). We observed mild clawing in both hands along with Wartenberg's sign (Figure 1B). In both upper limbs adduction, abduction, extension of fingers were weak (MRC grade 3+) other than thumb. In thumb adduction, abduction, extension and opposition were normal. Wrist adduction was weak (MRC grade 4) but grip was normal. Writing, buttoning and counting were preserved as well as elbow flexion and extension in both upper limbs. His deep tendon reflexes in both upper limbs were diminished or hypoactive and Hoffman's sign was absent. There was no sensory disturbance including spinothalamic and posterior column functions. Motor and sensory system examinations were preserved in both lower limbs including deep tendon reflexes and planter response. There was no nerve thickening and his cranial nerves were also intact including tongue and bulbar function. Neck movements were also not restricted.



A B

Fig.-1: *(A) Marked hypothenar (medial hand) and medial forearm atrophy with preservation of thenar (lateral hand eminence; (B) Mild clawing of both hands.*

We performed MRI of Cervical spine (both neutral and flexed position) with screening of whole spine along with NCS and EMG of all four limbs. Cervical MR images in neutral position showed focal atrophy of lower cervical cord at the C5-C7 vertebral levels without intramedullary abnormal high signal intensity (Figure 2A, 2B & 2C). When the neck was ûexed, the posterior wall of the cervical dural sac between C5 and D1 vertebral levels was seen to shift anteriorly. The markedly ûattened and anteriorly displaced cervical cord was compressed over the posterior surface of the C5 to D1 vertebral bodies (Figure 2D).

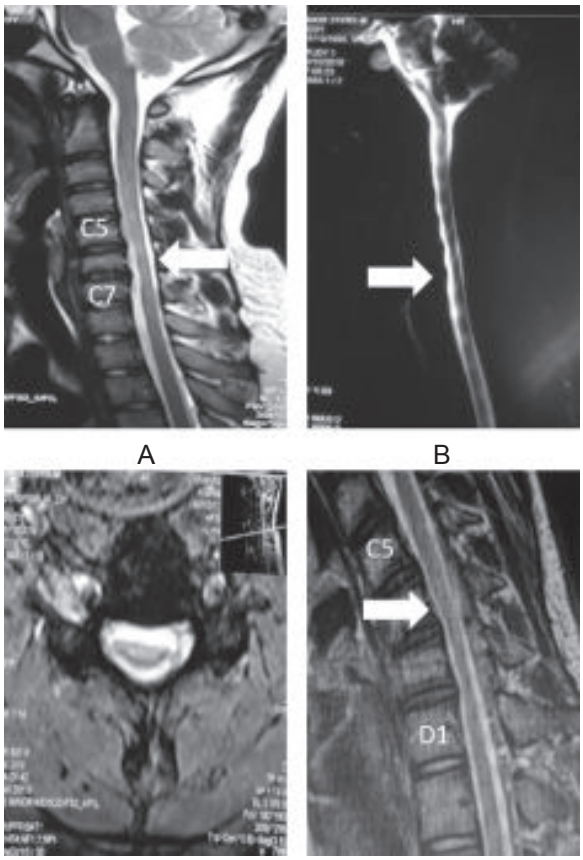


Fig.-2: *MRI of cervical spine. T2 sagittal (A & B) section showing focal cord atrophy (C5-C7 vertebral level), T2 axial © section showing marked anterior-posterior flattening of cord, T2 sagittal in flexed position (D) showing posterior dural sac shifting anteriorly with flattened cord compression against posterior surface of C5 to D1 vertebral bodies.*

NCS of both upper limbs showed marked reduction of CMAP (compound muscle action potential) amplitude recorded over ADM than that of APB (Figure 3). But conduction velocity and distal latency were normal in both median and ulnar nerves. EMG showed high amplitude, normal durationMUAPs (motor unit action potential) with reduced recruitment in 1st dorsal interosseous, pronator teres, biceps and flexor carpi ulnaris without any features of denervation (positive sharp waves, fibrillations). NCS and EMG of both lower limbs revealed normal. On the basis of MRI and Electrophysiological features Hirayama disease was diagnosed. The CMAP amplitude recorded over ADM (right: 0.64 mV and left: 1.030 mV; normal: ≥5.5 mV) was greatly reduced than that of APB (right: 16 mv and left: 16.90 mV; normal: e"4 mV) with ADM/APB ratio 0.04 (right) and 0.06 (left). So, electrophysiological correlation of reverse split-hand was assumed. For therapeutic purpose cervical collar was advised to prevent further flexion induced injury. Patient was also advised to take neurosurgical consultation.

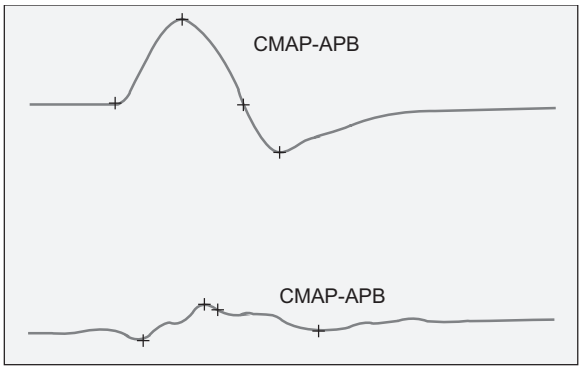


Fig.-3: *Marked reduction of CMAP amplitude recorded over ADM than that of APB.*

Discussion:

Since 1959 after description of the disease by Hirayama, it is being increasingly reported from many parts of the world but most notably from Asian subcontinent[1, 2,4-9, 11]. It is relatively benign in course and less disabling. Moreover there remains hopeful intervention maneuver. So it should be differentiated from ALS which is a relentlessly progressive neurodegenerative disorder with early fatal outcome.

In ALS split-hand syndrome is considered to be an early and important clinical sign where lateral hand (thenar-APB) is more affected with relative preservation of medial hand (hypothenar-ADM). The exact opposite phemenon was observed in HDand considered to be reverse split-hand. But this dissociated hand muscle atrophy in HD has got poor attention and not been studied systematically rather a very few studies are there[12, 13]. On the other hand split hand in ALS is now a focus of intense investigation[14, 15]. But reverse split-hand syndrome and its electrophysiological measuremay help to differentiate HD from ALS to a great extent.

The exact mechanism of reverse split-hand in Hirayama disease remains to be elucidated. Based

on some previous reports, ischemic/venous congestive myelopathy may damage selectively the hypothenar innervated anterior horn cells (AHC)[15]. According to several MRI studies disproportionate rate of growth between spine and dural sac causes dynamic flexion induced myelopathy. Dynamic anterior shift of dura in flexion results in cord compression, inducing microcirculatory disturbances and necrosis of the anterior horns, which are most vulnerable to ischaemia. As anterior dural shift is prominant at C6 vertebral level, the lower cervical spinal cord suffers maximum dynamic compression. This finding may explain the maximum denervation seen in C7 to T1 spinal myotomal levels and preferential involvement of ADM is the result of C8 myotomal involvement due to possible maximum cord compresson at C8 myotomal level[16, 17].

Currently HD is diagnosed on the basis of specific clinical features and MRI findings.Standards of clinical features described by Tashiro et al.help to identify and diagnose this condition are predominant distal muscle weakness with hand and forearm atrophy,unilateral upper limb involvement, age of onset between 10 to early 20s, insidious onset and gradual progression for several years then stabilizes, no lower extremity involvement, no irregular sensory disturbances or tendon reflexes and other disease excluded[18]. Suggestive MRI findings in neutral position are focal lower cervical cord atrophy with or without increased intramedullary signal intensity and crescent shaped lesion in the posterior epidural space of lower cervical cord. Flexion MRI shows anterior shift of posterior dural sac and compression of cervical cord to posterior surface of lower cervical vertebral bodies with corresponding post contrast high intramedullary signal intensity indicatingischemia[19].Besides these electrophysiology is done to exclude other differentials most notably ALS and myotonic dystrophy.

Previously several studies were done to see diagnostic accuracy of ADM/APB ratio in HD. In 2017 Kalita et al. showed ADM/APB ratio of <0.86 with 80.4% sensitivity and 86.3% specificity[20]. Jin et al. in 2014 found ADM/APB ratio<0.6 in 61% of HD patients and 2% patients with ALS[21]. In another study conducted by Kim et al. in 2015 found the ratio <0.6 in 46.7% HD patients and 3.6% ALS patients[22]. In our case we found ADM/APB ratio 0.04 in right hand and 0.06 in left hand which was consistent with previous studies.

As flexion induced injury of lower cervical cord is considered to be responsible for HD, wearing of cervical collar is the first line treatment option. In more advanced and severe functional disability surgical option like duroplasty with tenting has been performed with improved success rate and prognosis.

Conclusion:

Reverse split hand and its electrophysiological measure as ADM/APB ratio may prove important diagnostic tool in HD besides specific MRI features. It may also be used to differentiate it from ALS which is important as there are therapeutic and prognostic discrepancy. But relative study in this field is warrented.

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Bangladesh Journal of Neuroscience 2019; Vol. 35 (2): 115-118

A Case of Subcortical Band Heterotopia Presented with Epilepsy and Speech Regression.

MAHMUD R[1], GIAS UDDIN KM[2], RASSEL MA[3].

Abstract:

Subcortical Heterotopia is a rare developmental disorder of human brain due to mutation in the DCX or LIS1gene.It is predominantly a disease of female. It usually present with refractory seizure and varying degree of mental retardation. Here a case of 22 years lady who presented with refractory seizure is reported. Her MRI revealed Double cortex and her EEG revealed Frontal intermittent rhythmic delta activity (FIRDA).

Key word: *Seizure, Subcortical Band Heterotopia.*

Introduction:

Subcortical Heterotopia is a rare developmental disorder of human brain. It is of three types (a) Nodular (b) Laminar and (c) subcortical band heterotopia.[1, 2]. Subcortical band heterotopia is characterized by presence of bilaterally symmetrical, heterotopic grey matter which is located between the ventricles and the cortex[3]. It is the classic malformations associated with deûcient neuronal migration.[4]

Mutations in the *DCX* or *LIS1*gene are the predominant cause subcortical band heterotopia Altered structure or function of the proteins produced by the *DCX* or *LIS1*gene impairs important interactions that are needed for neuronal migration. Without proper neuronal migration, neurons in the developing brain can be misplaced, forming abnormal bands of tissue beneath the cerebral cortex[5, 6].

We are going to present the first case in Bangladesh from Kamrangirchar Dhaka, who was admitted in Neurology Department, Dhaka medical college with poorly controlled seizure, speech regression and finally diagnosed as double cortex syndrome.

Case report:

Miss Shila a 22 years old lady presented with recurrent seizure since her 5 years of age. The seizure started in right hand then became generalized. The seizure persisted for 2-3 minute. There was no preceding Prodrome, aura or automatism. There was post ictal confusion but no post ictal paralysis. She also had speech regression after 2 years of the onset of seizure. She had occasional rage attack. At the time of presentation she experienced 5-10 attacks per day.

She was on sodium valproate, carbamazepine and levetiracetam. Still the seizure was poorly controlled. Her mile stone of development was normal up to 6 years of age except she had mild mental retardation. There was no family history of Epilepsy. Patient is apathetic, non-communicating initially. There was no focal weakness. Superficial and deep tendon reflexes were normal. MRI revealed a band of grey matter located deep to, and roughly paralleling, the cortex, with pachygyric overlying cortex. The band of abnormal grey matter is complete. There is posterior predilection. EEG revealed bi-frontal intermittent rhythmic delta activity. We gradually discontinue carbamazepine, built up the doses of sodium valproate and add Clobazam. After 15 days her seizure was fully controlled. She began to speak and communicate.

1. Dr. Reaz Mahmud, Assistant Professor, Department of Neurology, Dhaka medical College.
2. Kazi Mohammad Gias Uddin, Associate professor and Head, Department of Neurology, Dhaka Medical College.
3. Dr. Mohammad Aftab Rassel, MD thesis student, Department of Neurology, Dhaka medical College.

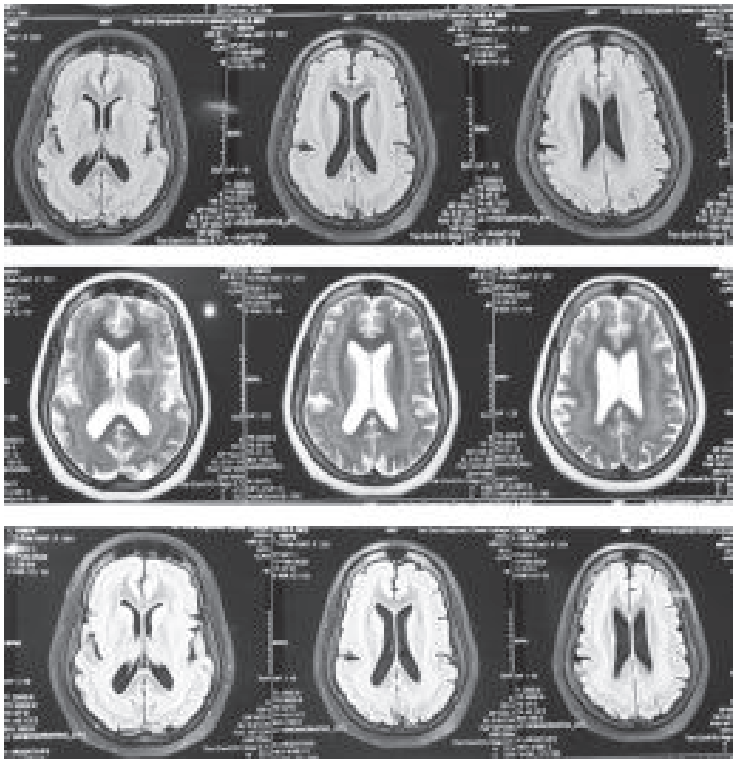

Fig.-1: *MRI of Brain T1 T2 FLAIR sequence revealed a band of grey matter located deep to, and roughly paralleling, the cortex, with pachygyric overlying cortex. The band of abnormal grey matter is complete. There is posterior predilection.*

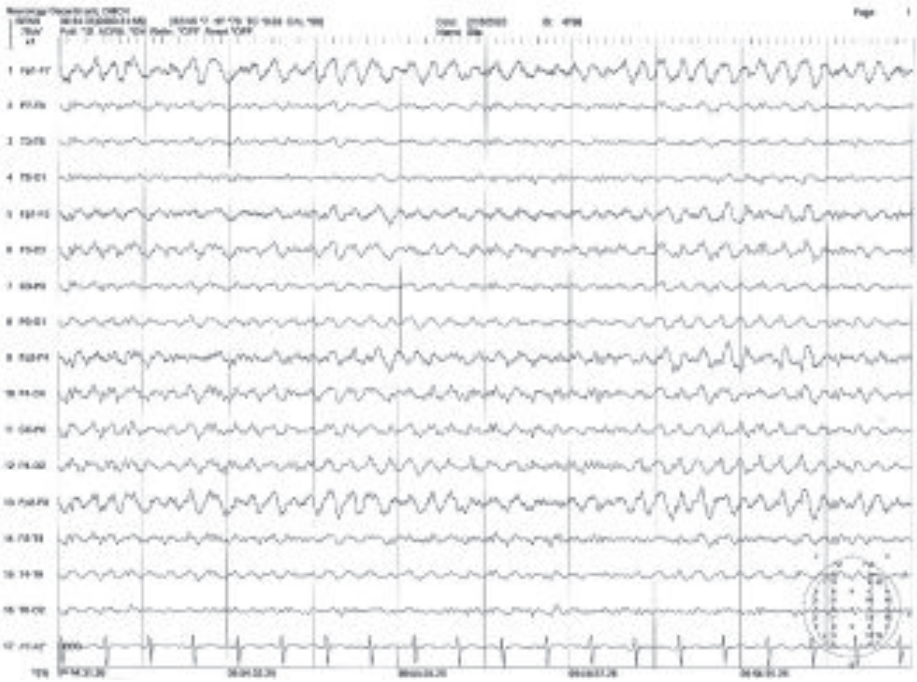

Fig.-2: *EEG in bipolar montage revealed Bi-Frontal intermittent rhythmic delta.*

Discussion:

It is found that most individuals with subcortical band heterotopia have *DCX* or LIs1gene mutations. IT is an X-linked dominant disorder. So SBH shows a striking skewing of sex ratio to females. As *DCX* is carried on the X chromosome of males. Mutations in *DCX* will usually have classical Lissencephaly in male whereas females have SBH[4]. The onset of the disease may occur at any age, predominantly in the 1st decade but occasionally delayed until the second or third decade.[3]

Our patient was a female who presented at 6 years of age.

Patients with SBH will usually have mild-to-moderate intellectual disability and a mixed seizure disorder. Intellectual disability is wide with severity roughly correlating with the thickness of the heterotopic band[3, 4].

The seizure types are highly variable from patient to patient, and vary from focal onset seizures (partial seizures) to generalized onset seizures. Simple/complex partial seizures are most often described (68%-69%). Drop attacks (26%-30%), absence seizures (23%-29%), and myoclonic seizures (14%-16%) are frequently found alone or in combination (43%-60%). generalized tonic-clonic seizures fond in19%-57%cases. Patients with West syndrome and Lennox–Gastaut syndrome have also been described. Importantly, a high proportion of drug resistance (65%-78%) is reported, and surgical treatment yields poor outcomes.[5, 7].

Those with more severe MRI abnormalities have significantly earlier seizure onset and are more likely to develop Lennox-Gastaut syndrome.[8]

This patient presented with mild mental retardation with poorly controlled seizure. There after she also developed speech regression. So our initial diagnosis was Landau Kleffner syndrome. Carbamazepine was thought to be the factor for worsening her seizure frequency. So it was decided to gradually withdraw carbamazepine and build up the dose of sodium valproate. To rule out any secondary etiology MRI of brain with contrast was advised.

In case of SBH MRI of shows the characteristic appearance of a smoothly marginated layer of gray matter coursing parallel to the lateral ventricle, separated from the overlying cortex and under-lying ventricle by layers of white matter. Bands are nei-ther convoluted nor contiguous with the overlying cortex. They do not contain blood vessels or CSF. The thicker the band of heterotopic neurons; the worse the disability and increased prevalence of developmental delay.[9]

The MRI of brain of the patient revealed a typical double cortex syndrome. The thickness or her band was mild which correlate her presentation. Her EEG revealed FIRDA. Her genetic testing could not be done due unavailability of the testing facilities. In MRI there is posterior dominance, so it cold be LIS1 Mutation.

After the adjustment of the dose of the drugs her seizure was fully controlled and her speech was regained.

Conclusion:

In dealing with a patient with epilepsy syndrome or epileptic encephalopathy MRI of brain should be mandatory. Adding and adjustment of the antiepileptic drug should also be rational. We have to be careful of adding carbamazepine in this type of the patient

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