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CONTENTS

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ORIGINAL ARTICLES

Association of Serum Ceruloplasmin Level with Parkinson's's Disease

ISLAM MZ[1], BARMAN KK[2], HABIB MA[3], ISLAM MR[4], HASANM[5], ISLAM MS[6], HUQ MR[7], SARKER I[8], AGARWALLA AK[9]

bstract:

Background: *Parkinson's disease, though a common neurodegenerative disease, is still elusive regarding its pathobiology. Neuronal degeneration in the midbrain substantia nigra by excess oxidative stress may play a role. As ceruloplasmin (Cp), a plasma protein is important to maintain intracellular iron homeostasis and reduce cellular oxidative stress, decreased serum Cp level may be an important factor in the pathogenesis of Parkinson's disease.* ***Methods:*** *This case-control study was conducted in the department of Neurology, BSMMU. Forty-five Parkinson's disease patients and equal number of controls were selected. Serum ceruloplasmin level was measured in the department of Biochemistry and Molecular Biology, BSMMU.* ***Results:*** *Mean serum Cp level was significantly lower (p-value <0.001) in case (27.64 mg/dl) than in control group (33.10 mg/dl).* ***Conclusion:*** *The association of low serum Cp level with Parkinson's disease may indicate a possible iron homeostasis abnormality as a pathogenic factor in Parkinson's disease.*

Keywords: *Parkinson's disease, Ceruloplasmin, Substantia nigra etc.*

Introduction:

Parkinson's disease (PD), a common neurodegenerative disease, is a clinical syndrome with variable combination of tremor, rigidity, bradykinesia and postural instability.PD is the second most common neurodegenerative disorder after Alzheimer disease[1]. Among general population the worldwide prevalence of PD was approximately 0.3 percent in a meta-analysis of 47 studies[2].

Although the majority of cases are sporadic, genetic factors play an important role in the pathogenesis, particularly when symptom appear before the age of 40 years[3].Pathologically PD is characterized by degeneration of dopaminergic neurons in the substantia nigra of the midbrain. An intracytoplasmic neuronal inclusion known as Lewy body, made up mainly of alpha-synuclein and ubiquitin, is the pathologic hallmark[4].Genetic factors along with abnormalities in protein processing, oxidative stress, mitochondrial dysfunction, excitotoxicity and other unknown mechanisms are probably involved in the pathogenic process[5]. Several evidences support disruption of iron metabolism as a key mechanism involved in neuronal death in PD[6]. Excess nigral iron deposition in PD using magnetic resonance based highly sensitive susceptibility weighted imaging was also demonstrated[7].

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Ceruloplasmin (Cp), an alpha-glycoprotein, is mainly synthesized in liver and plays an important role in cellular iron homeostasis. Decreased Cp activity in brain leads to intracellular iron accumulation, increasing oxidative stress which leads to cell death[8]. As Cp readily crosses blood-brain barrier, Cp level in serum is in equilibrium with brain Cp level and serum Cp level reflects the Cp activity in brain. It may be used as a biomarker for diagnosis of early PD when classical motor features have not yet developed[7].

As an indicator of cellular iron dis It may also facilitate the advent of iron chelation therapy as a disease modifying treatment option in PD patients[9]. Direct ceruloplasmin administration is also reported to be helpful in improving PD symptoms in some studies recently in animal models[10].

Methods:

This case-control study aimed to assess the association of serum ceruloplasmin level with Parkinson's disease. It was conducted in the department of Neurology, BSMMU in the time period of June, 18 to September, 19. Ethical clearance was taken from the institutional review board, BSMMU. Calculated 45 cases (Parkinson's disease diagnosed by Movement Disorder Society clinical diagnostic criteria, 2015) and equal number of controls (non-Parkinson'sian age and sex matched subjects) were selected via purposive sampling method. Patients of Wilson disease, chronic liver disease, chronic kidney disease, pregnant women or patients with active infection or inflammation were excluded. Serum ceruloplasmin level was measured by using Beckman Coulter-AU680 automated analyzer in thelaboratory of the department of Biochemistry and Molecular Biology, BSMMU. The mean and standard deviation of serum ceruloplasmin level of both case and control groups were calculated. Quantitative data were analyzed by Student's t-test and qualitative data were analyzed by χ^2 test. P value <0.05 was considered as statistically significant. Statistical analysis was done by SPSS software.

Results and Discussions:

In this study the mean age of case and controlgroups were respectively 57.8 and 58.0 years. Majority of the patients belonged to 50-80 years of age.Among the study population 68.9% were male and 31.1% were female in the case group(male: female = 2.2:1). Rahman et al. (2018) found 2.6 times male predominance in their study in Bangladesh.

Table-I

Demographic characteristics of the study population

Variables	Case (n=45)	Control (n=45)
Mean age (years)	57.8	58
Gender		
Male	31 (68.9%)	29 (64.4%)
Female	14 (31.1%)	16 (35.6%)

Serum ceruloplasmin level was significantly lower in case (27.64 mg/dl) than in control (33.10 mg/dl) group. This finding is similar to the studies by Jin et al.[7], Ling and Bhidayasiri[11], Nikam et al.[12], Song et al.[13] and Torsdottir et al.[14].

As a neurodegenerative disease of unknown etiology, PD has no established disease-modifying treatment option so far. As low serum ceruloplasmin may have a role in the pathogenesis of PD due to disturbance in brain intracellular iron accumulation and consequent oxidative stress, this finding may open a window forinvention of disease-modifying therapy for PD. Intravenous ceruloplasmin infusion and iron chelation therapy have been proposed and are under trial with initial success[15].

Table-II

Serum ceruloplasmin level in the study subjects

Serum ceruloplasmin (mg/dl)	Case (n=45) no. (%)	Control (n=45) no. (%)	p-value
Mean± SD	27.64±6.09	33.10±7.63	<0.001[s]
Range	(17-43) mg/dl	(21-49) mg/dl	

Conclusion:

The mean serum ceruloplasmin (Cp) level in Parkinson's disease (PD) patients was significantly lower than that of the control group. The study was conducted in a single center within a short time. Long term, multicentered, prospective study may further help confirm the association.

References:

1. Langston JW. The Parkinson's's complex: Parkinson'sism is just the tip of the iceberg. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2006 Apr;59(4):591-6.
2. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's's disease: A systematic review and meta analysis. Movement disorders. 2014 Nov;29(13):1583-90.
3. Singleton AB, Farrer MJ, Bonifati V. The genetics of P arkinson's disease: Progress and therapeutic implications. Movement Disorders. 2013 Jan;28(1):14-23.
4. Bezard E, Gross CE, Brotchie JM. Presymptomatic compensation in Parkinson's's disease is not dopamine-mediated. Trends in neurosciences. 2003 Apr 1;26(4):215-21.
5. Jellinger KA. Cell death mechanisms in Parkinson's's disease. Journal of neural transmission. 2000 Jan 1;107(1):1-29.
6. Jiang H, Wang J, Rogers J, Xie J. Brain iron metabolism dysfunction in Parkinson's's disease. Molecular neurobiology. 2017 May 1;54(4):3078-101.
7. Jin L, Wang J, Zhao L, Jin H, Fei G, Zhang Y, Zeng M, Zhong C. Decreased serum ceruloplasmin levels characteristically aggravate nigral iron deposition in Parkinson's's disease. Brain. 2010 Nov 24;134(1):50-8.
8. Weinreb O, Mandel S, Youdim MB, Amit T. Targeting dysregulation of brain iron homeostasis in Parkinson's's disease by iron chelators. Free Radical Biology and Medicine. 2013 Sep 1; 62:52-64.
9. Grolez G, Moreau C, Sablonnière B, Garçon G, Devedjian JC, Meguig S, Gelé P, Delmaire C, Bordet R, Defebvre L, Cabantchik IZ. Ceruloplasmin activity and iron chelation treatment of patients with Parkinson's's disease. BMC neurology. 2015 Dec;15(1):74.
10. Ayton S, Lei P, Duce JA, Wong BX, Sedjahtera A, Adlard PA, Bush AI, Finkelstein DI. Ceruloplasmin dysfunction and therapeutic potential for Parkinson's disease. Annals of neurology. 2013 Apr;73(4):554-9.
11. Ling H, Bhidayasiri R. Reduced serum caeruloplasmin levels in non-Wilsonian movement disorders. European neurology. 2011;66(3):123-7.
12. Nikam S, Nikam P, Ahaley SK, Sontakke AV. Oxidative stress in Parkinson's's disease. Indian Journal of Clinical Biochemistry. 2009 Jan 1;24(1):98-101.
13. Song YS, Kim JM, Kim KJ, Yun JY, Kim SE. Serum ceruloplasmin and striatal dopamine transporter density in Parkinson's disease: Comparison with 123I-FP-CIT SPECT. Clinical nuclear medicine. 2017 Sep 1;42(9):675-9.
14. Tórsdóttir G, Kristinsson J, Sveinbjörnsdóttir S, Snaedal J, Jóhannesson T. Copper, ceruloplasmin, superoxide dismutase and iron parameters in Parkinson's's disease. Pharmacology & toxicology. 1999 Sep; 85:239-43.
15. Belaidi AA, Bush AI. Iron neurochemistry in Alzheimer's disease and Parkinson's's disease: targets for therapeutics. Journal of neurochemistry. 2016 Oct; 139:179-97.

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Association of Serum Lipid Levels with Parkinson's Disease: A Case-Control Study

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Abstract:

Background: *Parkinson's disease (PD) is a common neurodegenerative disorder. Many hypotheses have been put forward for PD pathogenesis including role of lipid metabolism.* ***Methods:*** *This case control study was carried out in the department of neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from April 2018 to September 2019. A total of 90 persons were enrolled as study population after satisfying inclusion and exclusion criteria. Among them, 42 PD patients were grouped as cases and 48 healthy persons were controls.* ***Results:*** *We have compared the mean (±SD) value (mg/dl) of serum lipid variables among the cases and the controls. Serum total cholesterol in PD patients was found lower than that of control group (176.88 ± 41.12 vs 209.27 ± 43.69 mg/dl) which was statistically significant (p = 0.001) and mean (±SD) value (mg/dl) of serum LDL-C in PD patients was also found significantly lower than that of control group (107 .44 ± 39.04 vs 127.40 ± 37.83 mg/dl, p = 0.017). Serum TG levels were also significantly lower among PD patients than that of controls (152.40 ±77.86 vs 206.71 ±94.76 mg/dl, p = 0.04). Serum high-density lipoprotein cholesterol (HDL-C) levels were statistically similar among cases and controls (39.81 ± 9.79 vs 39.33 ±12.21 mg/dl, p = 0.840).* ***Conclusion:*** *There is an association between low serum TC, LDL-C and TG levels with PD. Further prospective studies are necessary to confirm the association.*

Key words: *Parkinson's disease, lipid, cholesterol, triglyceride etc.*

Introduction:

Parkinson's disease (PD) is a progressive degenerative disease of brain, characterized by resting tremor, rigidity, bradykinesia and postural instability. In 2016, 6·1 million individuals worldwide had Parkinson's disease, of whom 2·9 million (47·5%) were women and 3·2 million (52·5%) were men[1]. There were approximately 54198 (42488 to 67532) cases of PD in Bangladesh in 2016[1].

Nevertheless, the pathogenesis of PD is yet unknown. Although a few PD cases are due to several known genetic mutations, the disorder is largely idiopathic and likely involves interactions of the genome and the environment.

Cholesterol is an important constituent of cell membranes and plays a crucial role in the formation of the plasma membrane and signaling. Many neurodegenerative diseases are characterized by impaired cholesterol turnover in the brain. However, at which stage the cholesterol biosynthetic pathway is altered and how this contributes to pathogenesis remain unknown[2]. Several recent findings also

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suggest a role of lipid and cholesterol metabolism in Parkinson's disease pathogenesis[3]. High level of cholesterol may reduce the prevalence of PD by promoting the neuroprotective effect of CoQ10 since serum cholesterol is an important determinant of CoQ10 circulation[4].

Another possible mechanism behind association of serum lipid level with PD includes the role of APOE gene. A recent systematic review, however, demonstrated that it is the õ2 allele that is positively associated with higher prevalence of sporadic PD[5]. õ2 allele also has been associated with lower plasma LDL-C[6]. As APOE õ2 allele is associated with both PD and low plasma LDL-C, PD patients may have lower plasma LDL-C level. It was suggested in one study that these changes may be related to the reduced sympathetic activity in PD due to autonomic dysfunction. In that study, authors have found low TG levels in PD patients significantly in comparison to control group which might be consistent with reduced catecholamine and cortisol production[7].

The above mentioned evidences led us to formulate hypothesis that lower cholesterol may be associated with PD. Many studies have focused on the relationships between lipid profiles and the risk, as well as on the progression of PD. However, the results were not completely consistent with each other. Further studies are required to clarify the association of serum cholesterol level and neurodegenerative diseases including PD.

Methods:

After obtaining ethical clearance from Institutional Review Board (IRB) of BSMMU, patients having features of PD, diagnosed by MDS Clinical Diagnostic Criteria for PD, 2015[8] and fulfilling the inclusion and exclusion criteria were selected as case group. 42 patients were taken as cases; and 48 age and sex matched healthy persons were taken as controls who fulfilled the inclusion and exclusion criteria for control group. Sample size was calculated using mean and standard deviation of TC and LDL-C from a previous study using stastical formula at 5% level of significance and 90% power[9]. Demographic variables were age, sex, smoking status, presence of hypertension and body mass index (BMI). Serum lipid levels (TG, LDL-C, HDL-C, TG) were taken as laboratory variables. Informed written consent was taken from each patient or his/her attendant (both case and control group). After taking proper history, physical and neurological examinations, fasting serum lipid profile and other relevant investigations were done. Proper diagnosis and treatment were ensured for each person of case group. For fasting lipid profile, venous blood was collected under sterile conditions using a disposable syringe between 8.00 to 10.00 a.m. after overnight fasting (12 hours). The serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels were measured by using Beckman Coulter-A680 analyzer machine and low density lipoprotein Cholesterol (LDL-C) level was calculated by using Friedewald's equation from laboratory of the department of biochemistry, BSMMU. Quality control (QC) was ensured by doing updated calibration and by checking QC curve shown in the autoanalyzer.

The medical records, demographics, clinical and laboratory records of the all patients were examined. All the data were checked and edited after collection. At the end of data collection, the mean and standard deviation of serum levels of total cholesterol, HDL-C, LDL-C and TG were calculated for both case and control group. Quantitative data were analyzed by t test and qualitative data including sex, occupation, educational levels were analyzed by $\div^2$ test. P value <0.05 was considered as significant. In the case group, the correlation among serum cholesterol levels with disease duration was made by the Pearson's bivariate correlation test. Finally, to assess the relative significance of potential etiological variable, logistic regression was used for risk assessment. Odds ratios and 95% Confidence Intervals were calculated. All data processing statistical analysis were done by SPSS (Statistical Package for the Social Sciences) software (version 25.0).

Results:

Total 42 patients of Parkinson's disease were taken as cases and 48 age and sex matched healthy

persons were taken as controls. Results were expressed as mean ± SD. Unpaired '*t*' test was done as a test of significance. P <0.05 was considered as significant. Mean age of all patients was 59.43±11.34 years and mean age of control was 56.38±12.92 years. Distribution was statistically similar across cases and controls (p>0.05). Majority patients were male (73.8%) with 2.6:1 male-female ratio.Sex distribution was also similar across cases and controls (p>0.05). Serum TC, LDL-C and TG levels were significantly lower among PD patients than that of controls (p<0.05). Serum HDL-C levels were statistically similar among cases and controls. Logistic regression analysis was done to determine the Odds of developing PD in relation to different quartiles of cholesterol level adjusted for age, sex, BMI, HTN and smoking status. The lower the level of TC the higher the odds of developing PD.

Table-I

Sex distribution of participants (N=90)

Sex	Case (n=42) No. (%)	Control (n=48) No. (%
Male	31 (73.8)	35 (72.9)
Female	11 (26.2)	13 (27.1)

The lowest quartiles of LDL-C and TG also showed significant chance of developing Parkinson's disease. HDL-C didn't show any significant association with PD. Pearson's bivariate correlation was performed to asess correlation of serum lipid profile with duration of Parkinson's disease.None of the serum lipid profile variables showed any significant correlation with duration of disease.

Table-II

Distribution of participants according to their serum lipid profile (N=90)

Lipid profile	Case (n=42) (mean ± SD in mg/dl)	Control(n=48) (mean ± SD in mg/dl)	p-value
Total Cholesterol (TC)	176.88 ±41.12	209.27 ±43.69	0.001
Low Density Lipoprotein (LDL-C)	107.44 ±39.04	127.40 ±37.83	0.017
High Density Lipoprotein (HDL-C)	39.81 ±9.79	39.33 ±12.21	0.840
Triglyceride (TG)	152.40 ±77.86	206.71 ±94.76	0.004

Results were expressed as mean ± SD. Unpaired '*t*' test was done as a test of significance. P <0.05 was considered as significant.

Table-III

Correlation of serum lipid profile with duration of Parkinson's disease (N=42)

Correlation of duration of disease with PD	Pearson's r (correlation coefficient)	r^2 (coefficient of determination)	p-value
Total Cholesterol (TC)	0.046	0.002	0.772
Low Density Lipoprotein (LDL-C)	0.052	0.003	0.743
High Density Lipoprotein (HDL-C)	-0.225	0.051	0.153
Triglyceride (TG)	-0.295	0.087	0.058

Pearson's bivariate correlation was performed to compare between two groups. None of the serum lipid profile variables showed a significant correlation with duration of disease.

Table-IV

Odds ratios of Parkinson's disease according to quartiles of serum cholesterol concentrations (N=90)

Serum cholesterol	Unadjusted OR	95% CI		P value	Adjusted * OR	95% CI		P value
		Lower bound	Upper bound			Lower bound	Upper bound	
TC (mg/dl)								
224 – 342	1				1			
193 – 223	4.180	1.133	15.419	0.032	7.734	1.653	36.174	0.009
160 – 192	2.923	0.809	10.561	0.102	4.92	1.136	21.307	0.033
88 – 159	10.133	2.600	39.499	0.001	12.05	2.631	55.184	0.001
LDL-C (mg/dl)								
145 – 265	1				1			
115 – 144	1.259	0.377	4.204	0.708	1.387	0.366	5.262	0.63
87 – 114	1.574	0.491	5.046	0.445	2.297	0.613	8.603	0.217
40 – 86	4.048	1.21	13.538	0.023	3.957	1.059	14.777	0.041
HDL-C (mg/dl)								
18 – 32	1				1			
33 – 38	0.364	0.106	1.249	0.108	0.356	0.094	1.347	0.128
38 – 45	2.494	0.745	8.342	0.138	2.791	0.758	10.278	0.123
46 – 76	0.893	0.268	2.97	0.853	0.62	0.158	2.427	0.493
TG (mg/dl)								
220 – 502	1				1			
167 – 219	2.877	0.8	10.35	0.106	1.635	0.379	7.057	0.51
113 – 166	2.354	0.635	8.725	0.2	1.986	0.493	8.000	0.335
61 – 112	11.56	2.822	47.356	0.001	11.391	2.42	53.614	0.002

*Adjusted for age, sex, BMI, HTN and smoking status

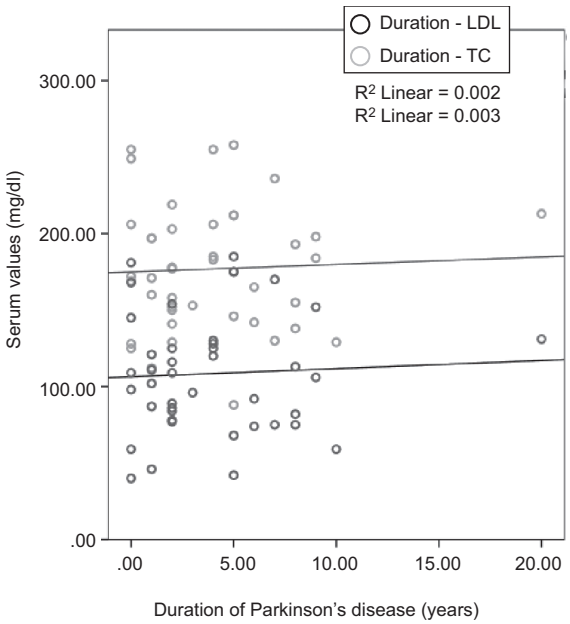

Figure 1: *Scatter diagram showing relationship of TC (green circles) and LDL (blue circles) with duration of PD (r^2 linear = coefficient of determination)*

Discussion:

Parkinson's disease is a common neurodegenerative disease having no definite treatment. Increasing evidence suggests that serum lipid levels are associated with PD, even may be related with pathogenesis of PD. This case-control study was carried out primarily with an aim to find out the association of serum lipid levels in patients with Parkinson's disease.

In this study mean ± SD values of serum total cholesterol and low density lipoprotein cholesterol level were reduced in PD patients as compared to those of control group (176.88 ±41.12 vs 209.27 ±43.69 mg/dl and 107.44 ±39.04 vs 127.40 ±37.83mg/dl respectively) which were statistically significant ($p<0.05$). Serum TG levels were also significantly lower among PD patients than that of controls (152.40 ± 77.86 vs 206.71 ± 94.76, $p = 0.04$). Serum high-density lipoprotein cholesterol (HDL-C) levels were statistically similar among cases and controls (39.81 ± 9.79 vs 39.33 ± 12.21, $p = 0.840$).

It was consistent with other case-control studies[7,9-13]. For example, in one study[13] the mean levels of total cholesterol, LDL-C and TG were significantly lower in the PD patients than in the controls (4.5 ± 0.9 mmol/L vs. 5.0 ± 0.9 mmol/L, p < 0.001; 2.5 ± 0.7 mmol/L vs. 2.9 ± 0.7 mmol/L, p < 0.001; 1.2 ± 0.8 mmol/L vs. 1.5 ± 0.8 mmol/L, p < 0.001; respectively. Like our study, most of the study didn't find any association of serum high-density lipoprotein cholesterol (HDL-C) with PD. All these studies including this one support the hypothesis that low serum lipids levels(TC, LDL-C, TG) could play an important role in the pathogenesis of Parkinson's disease.

We used a logistic regression analysis to get the effect of serum total cholesterol and low density lipoprotein cholesterol level on Parkinson's disease. Fasting concentrations of total cholesterol and LDL-C were divided into quartiles. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by logistic regression, adjusting for age, gender, smoking, BMI and presence of HTN. The lower the level of TC the higher odds of developing PD. Unadjusted odds ratios were 4.180, 2.923, 10.133 and adjusted odd ratios were 7.734, 4.92, 12.05 which were statistically significant (p <0.05). The lowest quartile of LDL-C also showed significant chance of developing Parkinson's disease. Unadjusted odds ratios were 1.259, 1.574, 4.048 and adjusted odds ratios were 5.262, 8.603, 14.777; the odds ratio of the lowest quartile was statistically significant (p <0.05). The lowest quartile of TG also showed significant chance of developing Parkinson's disease. Unadjusted odds ratios were 2.877, 2.354, 11.56and adjusted odds ratios were 1.635, 1.986, 11.391; the odds ratio of lowest quartile was statistically significant (p <0.05). HDL-C didn't show any significant association with PD.

It was consistent with some other recent studies[7,10,13]. Like current study, fasting concentrations of TC and LDL-C were divided into quartiles in another case-control study[10]. The risk of PD was significantly lower in the third tertile of cholesterol, triglyceride and total lipid levels than the first tertile in another study[7]. None of the serum lipid profile variables showed a significant correlation with duration of disease. Pearson's r (correlation coefficient) and p value for TC were 0.046 and 0.772 respectively; for LDL-C Pearson's r (correlation coefficient) and p value were 0.052 and 0.743 respectively which indicated no significant correlation. Serum TG and HDL-C showed negative but insignificant correlation. Also in a previous study, they did not find any significant correlations among TG, cholesterol, LDL-C, HDL-C and disease duration (p>0.05). It was found previously that PD patients have decreased incidence of stroke and myocardial infarction than healthy persons[14]. Low lipid TC, LDL-C and TG levels in PD patients may protect PD patients from adverse cardiovascular events.

Conclusion :

The present study showed that serum total cholesterol, low density lipoprotein cholesterol levels and triglyceride levels were significantly lower in PD patients in comparison to control group. This may be interpreted as linking lower TC, LDL-C and TG levels having association with PD. It seems timely and critical to reevaluate our results in larger scale in our population, and to seek the underlying mechanism that may be of potential importance in understanding the etiology of PD. Besides, it has public health implications, which may even lead to some changes in current guidelines recommending strict control of serum lipid profile.

References:

1. Dorsey ER, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC, Ansha MG, Brayne C, Choi JY, Collado-Mateo D, Dahodwala N. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2018 Nov 1;17(11):939-53.
2. Petrov AM, Kasimov MR, Zefirov AL. Cholesterol in the pathogenesis of Alzheimer's, Parkinson's diseases and autism: link to synaptic dysfunction. Acta Naturae (àíãëîÿçû÷íàÿ âåðñèÿ). 2017;9 (1 (32).
3. Hu G, Antikainen R, Jousilahti P, Kivipelto M, Tuomilehto J. Total cholesterol and the risk of Parkinson disease. Neurology. 2008 May 20;70(21):1972-9.

4. Kaikkonen J, Nyyssönen K, Tuomainen TP, Ristonmaa U, Salonen JT. Determinants of plasma coenzyme Q10 in humans. FEBS letters. 1999 Jan 29;443(2):163-6.
5. Huang X, Chen PC, Poole C. APOE-å2 allele associated with higher prevalence of sporadic Parkinson disease. Neurology. 2004 Jun 22;62(12):2198-202.
6. Bennet AM, Di Angelantonio E, Ye Z, Wensley F, Dahlin A, Ahlbom A, Keavney B, Collins R, Wiman B, de Faire U, Danesh J. Association of apolipoprotein E genotypes with lipid levels and coronary risk. Jama. 2007 Sep 19;298(11):1300-11.
7. Scigliano G, Musicco M, Soliveri P, Piccolo I, Ronchetti G, Girotti F. Reduced risk factors for vascular disorders in Parkinson disease patients: a case-control study. Stroke. 2006 May 1;37(5):1184-8.
8. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G. MDS clinical diagnostic criteria for Parkinson's disease. Movement Disorders. 2015 Oct;30(12):1591-601.
9. Cereda E, Cassani E, Barichella M, Spadafranca A, Caccialanza R, Bertoli S, Battezzati A, Pezzoli G. Low cardiometabolic risk in Parkinson's disease is independent of nutritional status, body composition and fat distribution. Clinical nutrition. 2012 Oct 1;31(5):699-704.
10. Huang X, Chen H, Miller WC, Mailman R, Woodard JL, Chen P. Lower LDL cholesterol levels are associated with Parkinson's disease: a case control study. Mov Disord. 2007;22(3):377-81.
11. Miyake Y, Tanaka K, Fukushima W, Sasaki S, Kiyohara C, Tsuboi Y, Yamada T, Oeda T, Miki T, Kawamura N, Sakae N. Case–control study of risk of Parkinson's disease in relation to hypertension, hypercholesterolemia, and diabetes in Japan. Journal of the neurological sciences. 2010 Jun 15;293(1-2):82-6.
12. Ikeda K, Nakamura Y, Kiyozuka T, Aoyagi J, Hirayama T, Nagata R, Ito H, Iwamoto K, Murata K, Yoshii Y, Kawabe K. Serological profiles of urate, paraoxonase-1, ferritin and lipid in Parkinson's disease: changes linked to disease progression. Neurodegenerative Diseases. 2011;8(4):252-8.
13. Guo X, Song W, Chen K, Chen X, Zheng Z, Cao B, Huang R, Zhao B, Wu Y, Shang HF. The serum lipid profile of Parkinson's disease patients: a study from China. International Journal of Neuroscience. 2015 Nov 2;125(11):838-44.
14. Nataraj A, Rajput AH. Parkinson's disease, stroke, and related epidemiology. Movement disorders: official journal of the Movement Disorder Society. 2005 Nov;20(11):1476-80.

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Short-Term Outcome in Patients with Acute Ischemic Stroke on the Basis of Admission Plasma D-Dimer Level

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Abstract:

Background: *Elevated levels of plasma D-dimer increase the risk of ischemic stroke, stroke severity, and the progression of stroke status, but the association between plasma D-dimer level and functional outcome is unclear.* ***Methods:*** *This observational cohort type of study was done in the Department of Neurology Dhaka Medical College Hospital, Dhaka during August, 2017 to July, 2019. Total 100 patients having acute ischemic stroke were included in this study. Age > 18 year of both male & female patients with first-ever acute ischemic stroke confirmed by CT scan/ MRI who gave informed written consent including consent to give blood sample for plasma D-dimer level measurement were enrolled in this study.* ***RESULTS:*** *Mean D-dimer level was 0.49±0.00 found in MRS 0, 0.57±0.19 in MRS 1, 0.49±0.00 in MRS 2, 0.70±0.33 in MRS 3, 1.46±0.77 in MRS 4, 1.60±0.59 in MRS 5 and 3.17±0.93 in MRS 6. The above findings indicate that MRS score increased with mean D-dimer significantly ($p<0.05$). Receiver-operator characteristic (ROC) was constructed by using D-dimer level, which gave a cut off value 1.7, with 90.9% sensitivity and 89.4% specificity for prediction of prognosis.* ***Conclusion:*** *Elevated plasma D-dimer level on admission was significantly associated with short-term poor outcome in patients with acute ischemic stroke.*

Keywords: *Ischemic stroke, D-dimer, MRS, Outcome etc*

Introduction:

Stroke is the second highest cause of death worldwide[1]. Approximately 15 million new acute stroke events occur every year and approximately 55 million people have had a stroke at sometime in the past. Two-thirds of these individuals live in the low & middle income countries [2]. According to the latest WHO data, death due to stroke in Bangladesh reached about 8.5% of total deaths[3]. Ischemic stroke is one of the major cause of death and places a tremendous burden on health resources. Timely intervention can dramatically improve outcome & reduce disability. D-dimer, the final product of plasmin-mediated degradation of fibrin-rich thrombi has emerged as a simple blood test that can be used in diagnostic algorithm for the exclusion of venous thrombo-embolism[4]. D-dimer level has certain advantages over other measures of thrombin generation because it's resistant to ex-vivo activation , relatively stable & has a long half-life[5] . It has been suggested that moderatetly elevated circulating D-dimer values reflect minor increases in blood coagulation , thrombin formation and turnover of cross-linked intravascular fibrin ; and these increases may be associated with coronary heart disease[6]. Patients with higher d-dimer levels are at higher risk of cardiovascular events even if they're receiving oral anti-coagulants[7]. Elevated D-dimer concentrations are of prognostic significance in

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long-term neurologic outcomes in childhood-onset arterial ischemic stroke[8]. Elevated D-dimer level has also been shown to relate to early clinical progression[9], stroke subtypes[10], infarction volume[11] and unfovourable outcome[12] in ischemic stroke patients .On the contrary , Haapaniemi and Tatlisumak, supposed that D-dimer level per se is not an independent predictor for poor outcome but reflects stroke etiology[13]. Thus, the purpose of this study is to find out the association between plasma D-dimer level at admission and short-term functional outcome in Bangladeshi patients with acute ischemic stroke.

Methods:

The study was carried out in the department of Neurology of Dhaka Medical college Hospital. Patients were collected from the departments of Neurology and Medicine. Following admission, patients with acute ischemic stroke was sorted out according to inclusion & exclusion criteria. History regarding demographic profile (age, sex); risk factors (hypertension, diabetes mellitus, smoking habit & alcohol abuse) and clinical presentation was noted on the questionnaire. At admission the neurological deficit was quantified using the National Institutes of Health stroke scale (NIHSS) .Under proper aseptic precautions blood sample was collected & sent for estimation of plasma D-dimer level to the laboratory of the Department of Hematology, Dhaka Medical College Hospital. The value of plasma D-dimer was considered for further analysis. Functional outcome of the patients was assessed with Modified Rankin Scale (MRS) by the principal investigator at day 90. Personal contact number of each patient was collected during interview. Subjects with incomplete data was excluded before final analysis.

Results:

Table VIII shows the distribution of the study patients by age. It was observed that almost one third (28.7%) patients belonged to age 50-59 years who were in alive group, but more than half (54.5%) of patients belonged to age 60-69 years were dead. The mean age was 59.97±12.41 years in alive and 64.27±6.68 years in death. The difference of age was statistically not significant (p>0.05) between two groups.

Table X shows the distribution of the study patients by risk factor. It was observed that majority (83.3%) patients had hypertension in alive and 15(68.2%) death, followed by 33(50.0%) DM in alive and 13(59.1%) in death, 21(31.8%) Hyperlipidemia in alive and 11(50.0%) in death, 20(30.3%) smoker in alive and 11(50.0%) in death and 3(4.5%) others in alive. The risk factors was statistically not significant (p>0.05) between two groups.

According to association between MRS score with D-dimer level it was observed that the mean D-dimer level was 0.49±0.00 found in MRS 0, 0.57±0.19 in MRS 1, 0.49±0.00 in MRS 2, 0.70±0.33 in MRS 3, 1.46±0.77 in MRS 4, 1.60±0.59 in MRS 5 and 3.17±0.93 in MRS 6. The above findings indicate that MRS score increased with the mean D-dimer level.

All patients were divided into two groups according to plasma D-dimer level. Patients having D-dimer level <1.5 μg/ml was considered as group I and D-dimer level ≥1.5 ìg/ml was considered as group II. Regarding the association between MRS with D-dimer level the mean MRS was 2.54±1.24 and 5.38±0.92 in D-dimer level <1.5 ìg/ml (Group I) and D-dimer level ≥1.5 ìg/ml (Group II) respectively, The mean MRS was significantly (p<0.05) higher in patients with D-dimer level ≥1.5 ìg/ml. On the other hand MRS belonged to 4 – 6 in 20.4% in group I and 97.1% in group II.

The area under the Receiver-operating characteristic (ROC) curve for prediction of prognosis is depicted in table XV. Based on the Receiver-operating characteristic (ROC) curve D dimer level had area under curve 0.972. Receiver-operating characteristic (ROC) was constructed by using D-dimer level, which gave a cut off value 1.7, with 90.9% sensitivity and 89.4% specificity for prediction of prognosis.

Table-I

Distribution of the study patients by age, survival and mortality (n=88)

Age	Alive (n=66)		Death (n=22)		P value
	n	%	n	%	
40-49	13	19.7	2	9.1	
50-59	19	28.7	0	0	
60-69	13	19.7	12	54.5	
70-79	14	21.3	8	36.4	
≥80	7	10.6	0	0	
Mean±SD	59.97±12.41		64.27±6.68		0.125^{ns}
Range (min-max)	40-85		47-70		

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

Table-II

Distribution of the study patients by risk factor, survival and mortality (n=88)

Risk factor	Alive (n=66)		Death (n=22)		P value
	N	%	n	%	
Hypertension	55	83.3	15	68.2	0.128^{ns}
DM	33	50.0	13	59.1	0.459^{ns}
Hyperlipidemia	21	31.8	11	50.0	0.124^{ns}
Smoking	20	30.3	11	50.0	0.093^{ns}
Others	3	4.5	0	0.0	0.308^{ns}

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

Table-III

Distribution of the study patients by MRS score with D-dimer level (n=88)

MRS score		D-dimer level	
	n	Mean±SD	Min-Max
0	2	0.49±0.00	0.49-.49
1	13	0.57±0.19	0.49-1.00
2	6	0.49±0.00	0.49-.49
3	23	0.70±0.33	0.35-1.50
4	16	1.46±0.77	0.49-2.90
5	6	1.60±0.59	1.00-2.30
6	22	3.17±0.93	1.50-4.50
P value		0.001^{s}	

s= significant, p value was reached from ANOVA test

Table-IV

Distribution of the study patients byMRS and plasma D-dimer level (n=88)

MRS	D-dimer level				P value
	Group-I (<1.5 μg/ml) (n=54)		Group-II (1.5 μg/ml) (n=34)		
	n	%	n	%	
0-3	43	79.6	1	2.9	
4-6	11	20.4	33	97.1	
Mean±SD	2.54±1.24		5.38±0.92		0.001[s]
Range(min-max)	0-5		3-6		

s= significant
p-value was reached from unpaired t-test.

Table-V

Receiver-operating characteristic (ROC) curve of D-dimer level prediction of prognosis.

	Cut off value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
D-dimer level	1.7	90.9	89.4	0.972	0.944	1.000

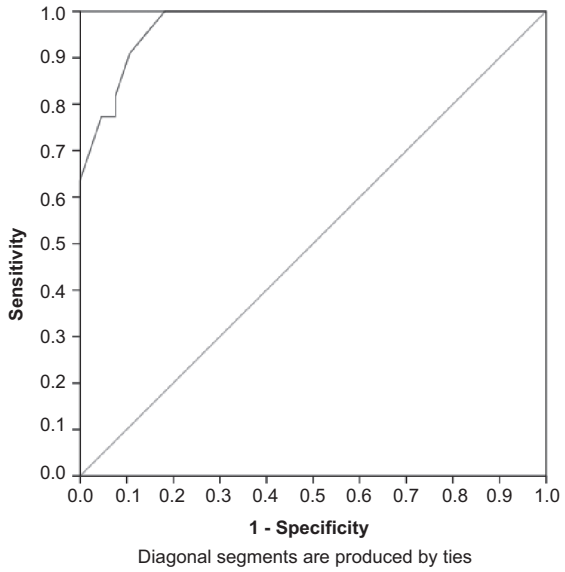

Fig.-1: *Receiver-operating characteristic (ROC) curve of D-dimer level prediction of prognosis.*

Discussion:

This observational study was carried out with an aim to assess the clinical presentation of the patients admitted with acute ischemic stroke and to observe the plasma D-dimer level on admission. This study also aimed to find out the short-term outcome of the patients according to Modified Rankin Scale (MRS) and to evaluate the relationship between plasma D-dimer level on admission and outcome of the patients at day 90.In this present study, it was observed that 28.4% patients belonged to age 60-69 years. The mean age was 61.05±11.38 years with ranged from 40 to 85 years. Yuan and Shi, (2014) find that themean age is 64.30 ± 11.71 years varied from 40 to 85 years which is consistent with the current study[14].In this current study, it was observed that 64.8% patients were male and 35.2% were female and male to female ratio was almost 2:1. Similarly, Yuan and Shifind acute ischemic stroke patients 64.70 % males and 35.30 % females, which is closely resembled with the present study[14]. In this current study, it was observed that the mean NIHSS score was11.8±5.49 with range from 1 to 23. Yang et al.[15]find the median NIHSS score on admission is 8 with in-terquartile ranges 5–11 points. Similar findings was also observed by Zhang et al.[16]

D-dimer—a marker of fibrin turnover—exhibits unique properties as a biological marker of hemostatic abnormalities and thrombosis [17]. Elevated D-dimer level is reportedly a determinant of the incidence of ischemic stroke not only in the general population but also in patients with atrial fibrillation (AF)[18]. In this present study, it was observed that the mean D-dimer level was 1.48±1.21 (ìg/ml) with range from 0.35 to 4.5(ìg/ml). Yang et al. study assesses plasma D-dimer levels with regard to their accuracy to predict short-term functional outcome in patients with AIS within 90 days in Chinese population and find the mean D-dimer level 1.36 ìg/ml varied from 0.55–3.11 ìg/ml, which is comparable with the current study[19].In this present study, It was observed that 26.1% patients belonged to MRS score 3. The mean MRS score was 3.64±1.79 with range from 0 to 6. Zhang et al. study observes an unfavorable functional outcome in 40.4% patients with a median MRS score of 4 having inter quartile range (IQR) 3 – 6[16]. In another study Barber et al. (2004) also find an unfavorable functional outcome in 31.4% with a median MRS score of 4 having inter quartile range IQR, 3–6[20]. In this current study, It was observed that 83.3% patients had hypertension in alive and 68.2% death, followed by 50.0% DM in alive and 59.1% in death, 31.8% Hyperlipidemia in alive and 50.0% in death, 30.3% Smoker in alive and 50.0% in death and 4.5% others in alive. The risk factorswas not statistically significant (p>0.05) between two groups. Similarly, Yang et al. studyobserves that 62.9% patients had hypertension in good outcomes and 87.0% poor outcomes, followed by 19.9% DM in good outcomes and 44.9% in poor outcomes and 21.2% Smoker in good outcomes and 20.3% in poor outcomes. The difference of age is statistically not significant (p<0.05) between two groups. Hypertension and DM are significantly higher in poor outcomes. Similar observations regarding the risk factors and prognosis are also observed by Zhang et al.According to association between MRS score with D-dimer level it was observed that the mean D-dimer level was 0.49±0.00 found in MRS 0, 0.57±0.19 in MRS 1, 0.49±0.00 in MRS 2, 0.70±0.33 in MRS 3, 1.46±0.77 in MRS 4, 1.60±0.59 in MRS 5 and 3.17±0.93 in MRS 6. This finding indicates that MRS score increased with mean D-dimer level significantly.

Patients those with MRS of <3 are predicted to have an independent life after stroke obtained by Sung et al.[21]. The investigators define MRS ≥3 as moderate to severe acute ischemic stroke. In this present study, all patients were divided into two groups. Patients having D-dimer level <1.5 ìg/ml was considered as group I and D-dimer level ≥1.5 ìg/ml was considered as group II. Regarding the association between MRS with D-dimer level the mean MRS was 2.54±1.24 and 5.38±0.92 in Group I and Group II respectively, The mean MRS was significantly (p<0.05) higher in patients with D-dimer level ≥1.5 ìg/ml (Group II). On the other hand MRS belonged to 4 – 6 in 20.4% in Group I and 97.1% in Group II. Yang et al. obtain in their study that functional outcome is assessed by the modified Rankin Scale (MRS), a favourable functional outcome is defined as a MRS of 0–2 points, whereas an unfavourable outcome is defined as a MRS of 3–6 points[19].

In this present study it was observed that in the Receiver-operator characteristic (ROC) curves D-dimer level had area under curve 0.972, which gave a cut off value 1.7, having 90.9% sensitivity and 89.4% specificity for prediction of prognosis in patients with acute ischemic stroke. Yang et al. study report that higher D-dimer level is associated with an unfavorable functional outcome compared with those in patients with a favorable outcome. After adjusting for all other significant outcome predictors, D-dimer predicts poor outcome. The optimal cut-off value of plasma D-dimer levels as an indicator for diagnosis of unfavorable functional outcome is projected to be 1.99 mg/L, which yields a sensitivity of 81.2% and a specificity of 79.7%, the area under the curve is 0.84 with 95%CI, 0.79–0.90, which are comparable with the current study. The investigators also mention that D-dimer levels increase per unit patients having poor outcome increased more than 4 times greater as compared with patients who survived. After adjustment for possible parameters, D-dimer level remains as an independent predictor for mortality with an OR of 3.22 having 95% CI, 2.05–6.43.Hamataniet al

mention in their study that neither in-hospital nor 30-day ischemic stroke events are observed in patients with D-dimer level less than the reference limit of normal (<1.0 ìg/mL)[22]. This cutoff value of 1.0 ìg/mL has a sensitivity of 100%, achieving a negative predictive value of 100%. Subgroup analyses show that D-dimer level is significantly associated with short-term ischemic stroke events in patients without atrial fibrillation OR=2.46; 95% CI, 1.39–4.54 for in-hospital ischemic stroke; and OR=2.20; 95% CI, 1.16–4.15 for 30-day ischemic stroke and those without antithrombotic therapy OR=2.79; 95% CI, 1.53–5.57 for in-hospital ischemic stroke; and OR, 2.45; 95% CI, 1.30–4.91for 30-day ischemic stroke. Saver and Altman et al. find the correlation coefficients between NIHSS and the MRS at admission is r=0.51[23]. Correlation analysis Sung et al. show a very significantly high correlation (r = 0.775) between NIHSS with MRS, index for severity of acute ischemic stroke and subsequent neurological impairment, respectively.

Conclusion:

This study has undertaken to determine the association between admission plasma D-dimer level and short-term outcome in patients with acute ischemic stroke. Acute ischemic stroke is more common in 60-69 years and above and male predominant. Hypertension, DM and hyperlipidemia are more common risk factor in Acute ischemic stroke and anterior circulation stroke is more common in this study. Age, sex, risk factors are not significantly associated with short-term outcome in patients with acute ischemic stroke. NIHSS score and D-dimer level are significantly elevated in patients with acute ischemic stroke patients having poor outcome. MRS score and D-dimer level are significantly associated. The mean MRS is significantly higher in patients with D-dimer level e 1.5 5ØÍÞg/ml. D-dimer level is a sensitive and specific predictive marker for short-term outcome in acute ischemic stroke. Therefore elevated plasma D-dimer level on admission is significantly associated with the poor prognosis in patients with acute ischemic stroke. There is a significant correlation found between NIHSS with MRS.

References:

1. WHO Fact sheet – The top ten causes of death (2015).
2. Indian economy overview, 2007
3. WHO Fact sheet (2011)
4. Meng, R, Wang, X, Hussain, M, Dornbos III, D, Meng, L, Liu, Y, Wu, Y, Ning, M, Ferdinando S, B, Lo, E.H. and Ding, Y. Evaluation of plasma D-dimer plus fibrinogen in predicting acute CVST. *International Journal of Stroke*, 2014; *9*(2), pp.166-73.
5. Haapaniemi, E and Tatlisumak,T. Is D dimer helpful in evaluating stroke patients? A systematic review. *Acta Neurologica Scandinavica*, 2009; *119*(3), pp.141-50.
6. Lowe, G.D and Rumley, A. Use of fibrinogen and fibrin D-dimer in prediction of arterial thrombotic events. *Thrombosis and haemostasis*, 1999;*82*(08), pp.667-72.
7. Mahe, I, Bergmann, J.F, Chassany, O, Simoneau, G, Drouet, L and COAGFA Group, A multicentric prospective study in usual care: D-dimer and cardiovascular events in patients with atrial fibrillation. *Thrombosis research*,2012; *129*(6), pp.693-99.
8. Goldenberg, N.A, Jenkins, S, Jack, J, Armstrong-Wells, J, Fenton, L.Z, Stence, N.V, Oleszek, J, Boada, R, Wilkening, G.N, Wilkinson, C and Soep, J.B. Arteriopathy, D-dimer, and risk of poor neurologic outcome in childhood-onset arterial ischemic stroke. *The Journal of pediatrics*, 2013; *162*(5), pp.1041-46
9. Yuan, W and Shi, Z.H. The relationship between plasma D-dimer levels and outcome of Chinese acute ischemic stroke patients in different stroke subtypes. *Journal of Neural Transmission*,2014; *121*(4), pp.409-13.
10. Koch, H.J, Horn, M, Bogdahn, U and Ickenstein, G.W. The relationship between plasma D-dimer concentrations and acute ischemic stroke subtypes. *Journal of Stroke and Cerebrovascular Diseases*,2005; *14*(2), pp.75-9.

11. Park, Y.W, Koh, E.J and Choi, H.Y. Correlation between serum D-dimer level and volume in acute ischemic stroke. *Journal of Korean Neurosurgical Society*,2011; *50*(2), p.89.

12. Berge, E, Friis, P and Sandset, P.M. Hemostatic activation in acute ischemic stroke. *Thrombosis research*,2001; *101*(2), pp.13-21.

13. Haapaniemi, E and Tatlisumak, T. Is D dimer helpful in evaluating stroke patients? A systematic review. *ActaNeurologica Scandinavica*,2009; *119*(3), pp.141-50.

14. Yuan, Wand Shi, Z.H. The relationship between plasma D-dimer levels and outcome of Chinese acute ischemic stroke patients in different stroke subtypes. *Journal of Neural Transmission*, 2014; *121*(4), pp.409-13.

15. Yang, X.Y, Gao, S, Ding, J, Chen, Y, Zhou, X.S. and Wang, J.E. Plasma D-dimer predicts short-term poor outcome after acute ischemic stroke. *PLoS One*,2014; *9*(2), p.e89756.

16. Zhang, J.L, Yin, C.H, Zhang, Y, Zhao, L.B, Fu, H.J and Feng, J.C. Plasma copeptin and long term outcomes in acute ischemic stroke. *ActaNeurologica Scandinavica*, 2013; *128*(6), pp.372-80.

17. Weitz, J.I, Fredenburgh, J.C. and Eikelboom, J.W. A test in context: D-dimer. *Journal of the American College of Cardiology*,2017; *70*(19), pp.2411-20.

18. Sadanaga, T, Sadanaga, M. and Ogawa, S. Evidence that D-dimer levels predict subsequent thromboembolic and cardio-vascular events in patients with atrial fibrillation during oral anticoagulant therapy. *Journal of the American College of Cardiology*, 2010; *55*(20), pp.2225-31.

19. Yang, X.Y, Gao, S, Ding, J, Chen, Y, Zhou, X..and Wang, J.E. Plasma D-dimer predicts short-term poor outcome after acute ischemic stroke. *PLoS One*,2014; *9*(2), p.e89756.

20. Barber, M, Langhorne, P, Rumley, A, Lowe, G.D and Stott, D.J. Hemostatic function and progressing ischemic stroke: D-dimer predicts early clinical progression. *Stroke*,2004; *35*(6), pp.1421-25.

21. Sung, P.H, Chen, K.H, Lin, H.S, Chu, C.H, Chiang, J.Y and Yip, H.K. The Correlation between Severity of Neurological Impairment and Left Ventricular Function in Patients after Acute Ischemic Stroke. Journal of clinical medicine, 2019; 8(2), p.190.

22. Hamatani, Y, Nagai, T, Nakai, M, Nishimura, K, Honda, Y, Nakano,H, Honda, S, Iwakami, N, Sugano, Y,Asaumi, Y and Aiba, T. Elevated Plasma D-Dimer Level Is Associated With Short-Term Risk of Ischemic Stroke in Patients With Acute Heart Failure. *Stroke*, 2018; *49*(7), pp.1737-40.

23. Saver, J.. and Altman, H. Relationship between neurologic deficit severity and final functional outcome shifts and strengthens during first hours after onset. Stroke,2012; 43(6), pp.1537-41.

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Cerebrospinal Fluid Protein Level and Nerve Conduction Study as Short-Term Prognostic Marker of Guillain Barré Syndrome

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Abstract:

Background: *Guillain Barré Syndrome (GBS) diagnosis is based on a combination of clinical features, Nerve conduction studies (NCS) and analysis of the cerebrospinal fluid (CSF) which eventually assist in monitoring disease progression as well as the efficacy of immunotherapy. The main objective of this study was to determine the relation of CSF protein level and nerve conduction study with short-term prognosis of GBS patients.* ***Methods:*** *This observational study was carried out in the Department of Neurology and Medicine, Dhaka Medical College Hospital, Dhaka during the period August, 2017 to July, 2018. Total 50 patients suffering from GBS were enrolled in this study. Lumber puncture (LP) and NCS were done at day 10 of symptom onset.* ***Results:*** *In this study majority (87.5%) of the patients had GBS Disability score <3 in demyelinating and 16(47.1%) in axonal on day 90. Three fourth (75.0%) patients EGRIS score was ³3 in demyelinating and 34(100.0%) in axonal and mEGOS it was revealed that more than two third (68.8%) patients mEGOS score was ³6 in Demyelinating and 33(97.1%) in axonal. More than three fourth (76.0%) patients ³6 mEGOS score in CSF protein <100 (mg/dl) and 25(100.0%) in CSF protein ³100 (mg/dl). Multiple logistic regression analysis showing a subject with axonal GBS had 1.579 (95.0% C.I 1.717 to 3.475), CSF Protein had 1.013 (95.0% C.I. 1.001 to 1.026) (PÂ0.05%).* ***Conclusion:*** *CSF analysis for protein and NCS examination appeared as the essential short term predictors in evaluating diagnostic accuracy and prognostic determinant of GBS early.*

Keywords: *NCS, CSF Protein, GBS disability score, EGRIS, mEGOS*

Introduction:

Guillain-Barré syndrome (GBS) is a post-infectious immune-mediated peripheral neuropathy characterised by rapidly progressive symmetrical weakness and sensory loss usually followed by slow clinical recovery with heterogeneous severity of neurological deficits and prognosis[1]. It is currently the most frequent cause of acute flaccid paralysis worldwide and constitutes one of the serious emergencies in neurology[2,3,4]. Statistical analyses reported the incidence of GBS in Western countries, mostly from Europe and North America, ranges from 0.89 to 1.89 cases per 100,000 populations per year[4,5]. GBS is typically triggered by antecedent infections presented as symptoms of upper respiratory tract infection or diarrhoea. Campylobacter jejuni is blamed for at least one-third of these infections, cytomegalovirus infections being the second most common[6].

Autoimmune response is the cardinal step in the development of GBS. There is a molecular mimicry

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between the lipooligosaccharides of the infectious agents and the gangliosides in human, ultimately affecting the myelin-protein sheathing and the axons themselves to various degrees[7]. These lead to segmental demyelination and axonal degeneration as well as infiltration of macrophages, lymphocytes and mast cells in the endoneurium of nerves in the peripheral nervous system which are found in nerve biopsy[8]. Nerve conduction studies (NCS) are the fundamental investigations to confirm the diagnosis and to assess the severity of the disease[9].

A new thought has been proposed recently and there many ongoing researches regarding the role of CSF studies as a prognostic marker of GBS. As GBS affects the peripheral nervous system, CSF is a potential source for biomarkers, since the CSF compartment is in close contact with the proximal nerve roots, where biochemical changes related to the disease are likely to be reflected[10]. Therefore the altered protein content of CSF due to various cerebrospinal fluid biomarkers, such as albumin, myelin basic protein, axonal damage markers (neurofilaments, tau and anti-ganglioside antibodies), glial and neuronal markers (neuron specific enolase, 14-3-3 proteins, S100B and hypocretin-1) is thought to mirror the damage within the tissue of the nervous system[11]. Moreover the dysfunction of B-CSF-B and BNB damage results in an alteration of CSF flow rate with influx of serum proteins into the CSF resulting in modulation of the protein content in CSF. Also the intra-thecal synthesis of proteins contributes to the changes of protein content in CSF. All these have been proposed the CSF protein could play a role as a marker for disease process, prognostic accuracy and treatment response[10,11]. In addition, electrophysiological studies on GBS patients have highlighted the prognostic value of early motor conduction studies[12]. Many studies regarding the role of CSF protein as a short-term prognostic marker have been conducted worldwide but no similar studies have been found in Bangladesh. Keeping the importance of the topic in mind the study has been designed to find out the role of CSF protein and motor NCS study in GBS.

Methods:

This study was carried out in the department of neurology, Dhaka Medical college hospital. A total of about 50 patients were included in the study following admission in department of neurology. A written informed consent was collected from each patient and interview has been taken by the researcher himself and verified by a consultant neurologist. A semi-structured questionnaire had been made consisting demographic profile, clinical presentation and comorbid disease. A special written consent was taken for lumbar puncture and with all aseptic precautions lumber puncture was done on day 10 of symptom onset. Following collection of CSF, sample was sent for study to the biochemistry laboratory of BSMMU. CSF protein estimation by using ultraviolet spectro-photometric method with a Atellica CH analyzer, Siemens, Germany and level of 45mg/dl was used as upper cutoff value. Patients were divided into two groups according to the presence of amount of protein. In addition, Nerve Conduction Studies of cross limb were done at day 10 and type of GBS was stratified into demyelinating and axonal group based upon the criteria suggested by Albers and Kelly by using Nihon Cohden Neuropack 2 system (Nihon Cohden Corp, Tokyo, Japan) maintaing the skin temperature at 32-34ÚC. Assessment of prognosis was done at day 10 of onset of symptom using EGRIS and mEGOS score and GBS disability score at admission and day 90 of symptom onset. Patients whose condition improved were discharged from hospital. Patients address and telephone number taken and contacted and advised for followed up at 90 days in Neurology Specialized Clinic, DMCH.

Results:

In this study, almost three fourth (76.0%) patients belong to age 18-25 years and almost three fourth (72.0%) patients were male and 14(28.0%) were female. By NCS findings, it was observed that more than two third (68.0%) patients had axonal and 16(32.0%) demyelinating.

Table I shows that more than two third (68.0%) patients had axonal and 16(32.0%) in demyelinating.

Table-I

Distribution of the study patients by NCS findings (n=50)

NCS findings	Number of patients	Percentage
Axonal	34	68.0
Demyelinating	16	32.0

Table II shows that more than half (52.9%) of the patients had GBS Disability score >3 in axonal and 2(12.5%) in demyelinating at day 90. The difference was statistically significant (p<0.05) between two groups.

Table III shows that three fourth (75.0%) patients EGRIS score was ≥3 in demyelinating and 34(100.0%) in axonal. The difference was statistically significant (p<0.05) between two groups.

Table IV shows that more than two third (68.8%) patients mEGOS score was ≥6 in Demyelinating and 33(97.1%) in axonal. The difference was statistically significant (p<0.05) between two groups.

Table V shows that more than half (61.8%) patients belonged to CSF protein ≥100 (mg/dl) in axonal and 4(25%) in demyelinating. The difference was statistically significant (p<0.05) between two groups.

Table VI shows that more than half (56.0%) patients had GBS disability score >3 on day 90 in CSF protein ≥100 (mg/dl), 6(24.0%) in CSF protein<100 (mg/dl). The difference was statistically significant (pÂ0.05) between two groups.

Table VII shows that all (100.0%) patients had EGRIS score ≥3 in CSF protein ≥100 (mg/dl) and 21(84.0%) in CSF protein <100 (mg/dl). The difference was statistically significant (pÂ0.05) between two groups.

Table VIII shows that more than three fourth (76.0%) patients had mEGOS score ≥6 in CSF protein <100 (mg/dl) and 25(100.0%) in CSF protein ≥100 (mg/dl). The difference was statistically significant (p<0.05) between two groups.

Table IX shows that a subject with axonal GBS had 1.579 (95.0% C.I 1.717 to 3.475), CSF Protein had 1.013 (95.0% C.I. 1.001 to 1.026), EGRIS had 0.659 (95.0% C.I. 0.355 to 1.224) and mEGOS had 1.172 (95.0% C.I. 0.415 to 3.31) times increase in odds, where only axonal GBS and CSF protein were statistically significant (P<0.05%).

Table X shows ROC curves based GBS Disability score on day 90, EGRIS and mEGOS which had area under curve (AUC) 0.910, 0.606 and 0.836. ROC curve was constructed by using GBS Disability score on day 90, EGRIS and mEGOS,

Table-II

Comparison of NCS findings with GBS Disability score at day 90 of admission of the study patients (n=50)

GBS Disability score at day	90 Demyelinating (n=16)		Axonal (n=34)		P value
	n	%	n	%	
<3	14	87.5	16	47.1	0.001[s]
≥3	2	12.5	18	52.9	

Table-III

Comparison of NCS findings with EGRIS score at day 10 of the study patients (n=50)

EGRIS score 10 at day	Demyelinating (n=16)		Axonal (n=34)		P value
	n	%	n	%	
<3	4	25.0	0	0.0	0.002[s]
≥3	12	75.0	34	100.0	

Table-IV

Comparison of NCS findings with mEGOS score at day 10 of the study patients (n=50)

mEGOS score	Demyelinating (n=16)		Axonal (n=34)		P value
at day 10	n	%	n	%	
<6	5	31.3	1	2.9	0.001[s]
≥6	11	68.8	33	97.1	

Table-V

Comparison of NCS findings with CSF protein of the study patients (n=50)

CSF protein	Demyelinating (n=16)		Axonal (n=34)		P value
(mg/dl)	n	%	n	%	
<100	12	75.0	13	38.2	
≥100	4	25.0	21	61.8	
Mean±SD	112.41	±33.32	139.56	±30.25	0.008[s]
Ranges(min-max)	48	-255	70	-273	

Table VI

Comparison of CSF protein with GBS Disability score at day 90 of admission of the study patients (n=50)

GBS disability	<100 (mg/dl)(n=25)		≥100 (mg/dl)(n=25)		P value
score at day 90	n	%	n	%	
<3	19	76.0	11	44.0	0.021[s]
≥3	6	24.0	14	56.0	

Table-VII

Comparison of CSF protein with EGRIS score at day 10 of the study patients (n=50)

EGRIS score	<100 (mg/dl) (n=25)		≥100 (mg/dl)(n=25)		P value
at day 10	n	%	n	%	
<3	4	16.0	0	0.0	0.037[s]
≥3	21	84.0	25	100.0	

Table-VIII

Comparison of CSF protein with mEGOS score at day 10 of the study patients (n=50)

mEGOS score	<100 (mg/dl)(n=25)		≥100 (mg/dl)(n=25)		P value
at day 10	n	%	n	%	
<6	6	24.0	0	0.0	0.009[s]
≥6	19	76.0	25	100.0	

Table-IX

Multiple logistic regression analysis showing the effect of independent variables on dependent variable

	OR	95% C.I.		P value
		Lower	Upper	
Axonal GBS	1.579	1.717	3.475	0.021[s]
CSF protein	1.013	1.001	1.026	0.038[s]
EGRIS	0.659	0.355	1.224	0.187[ns]
mEGOS	1.172	0.415	3.31	0.764[ns]

Table-X

Receiver-operator characteristic (ROC) curve of GBS disability score on day 90, EGRIS and mEGOS score

	Cut of value	Sensitivity	Specificity	AUC	95%Confidence interval (CI)	
					Lower bound	Upper bound
GBS Disability score on day 90	2.50	58.8	100.0	0.910	0.830	0.990
EGRIS	3.50	91.2	50.0	0.606	0.398	0.813
mEGOS	6.50	67.6	87.5	0.836	0.711	0.962

which gave a cut off value 2.50, 3.50 and 6.50 with 58.8%, 91.2% and 67.6% sensitivity and 100.0%, 50.0% and 87.5% specificity respectively for prediction of GBS patients.

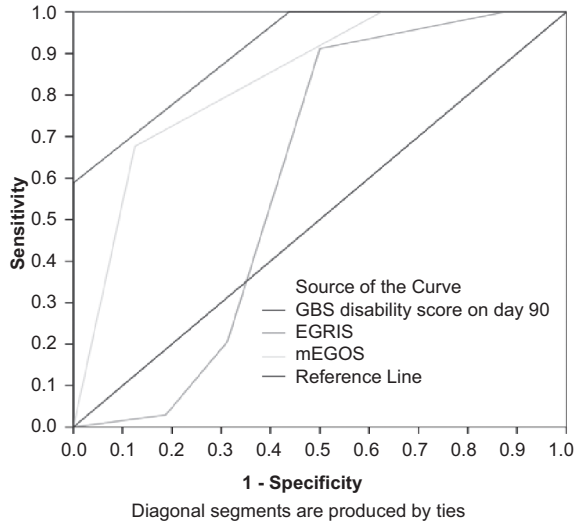

Fig.-1: *Receiver-operator characteristic (ROC) curve showing area under curve(AUC) of GBS Disability score on day 90, EGRIS and mEGOS score.*

Discussion:

In this study age distribution was found mostly in young age group because Bangladesh is a developing country, so there is infection specially campylobacter jejuni infection affect may be more in this age group. In our population axonal variety is most prevalent and different findings from western and European countries may be due to more prevalence of c.jejuni infection in our population due to cultural, environmental & climate factors. Regarding NCS findings all short term prognostic score i.e. GBS disability score, EGRIS score and mEGOS score showed that axonal variety was associated with high score and worse prognosis. Regarding CSF protein all short term prognostic marker also showed that increased protein was associated with high score and worse prognosis. According to ROC curve, it was shown that all the three scores are useable for the prediction of outcome of GBS but mEGOS score

is more acceptable because its sensitivity and specificity both is in acceptable range than other two score. In multiple logistic regression analysis showed that axonal GBS and increased CSF protein was independent prognostic factor of Guillain Barre´ Syndrome patients.

Conclusion:

Cerebrospinal fluid analysis for protein and Nerve conduction studies appeared as the essential short term predictors in evaluating diagnostic accuracy and the prognostic determinant of GBS early. However, the role of EGRIS score, mEGOS score and GBS disability score in categorization of different variants of GBS are also encouraging for formulating the futures strategies based on the unique scoring as revealed in this study. The data generated in this research will serve as baseline information in order to practice in neurological centers for assessment of the clinical stage and management of the critically ill crippling GBS patients. It can be said that the present study presents the role of increased CSF protein and Nerve conduction studies as prognostic markers of Guillain-Barré syndrome.

References:

1. Van Koningsveld R, Steyerberg EW, Hughes RA, Swan AV, van Doorn PA, Jacobs BC. A clinical prognostic scoring system for Guillain-Barré syndrome. The Lancet Neurology. 2007 Jul 1;6(7):589-94.
2. Shahrizaila N, Yuki N. Peripheral neuropathies: Clinical prognostic scales in Guillain–Barré syndrome. Nature Reviews Neurology. 2011 Jul;7(7):362.
3. Willison HJ, Jacobs BC, van Doorn PA. Guillain-barre syndrome. The Lancet. 2016 Aug 13;388(10045):717-27.
4. Yuki N, Hartung HP. Guillain–Barré syndrome. New England Journal of Medicine. 2012 Jun 14;366(24):2294-304.
5. Poropatich KO, Walker CL, Black RE. Quantifying the association between Campylobacter infection and Guillain-Barré syndrome: a systematic review. Journal of health, population, and nutrition. 2010 Dec;28(6):545.
6. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123-33.
7. Van Den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, Van Doorn PA. Guillain–Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. Nature Reviews Neurology. 2014 Aug;10(8):469.
8. Hughes RA, Cornblath DR. Guillain-barre syndrome. The Lancet. 2005 Nov 5;366(9497):1653-66.
9. Kerasnoudis A, Pitarokoili K, Behrendt V, Gold R, Yoon MS. Increased cerebrospinal fluid protein and motor conduction studies as prognostic markers of outcome and nerve ultrasound changes in Guillain–Barré syndrome. Journal of the neurological sciences. 2014 May 15;340(1-2):37-43.
10. Brettschneider J, Petzold A, Süssmuth S, Tumani H. Cerebrospinal fluid biomarkers in Guillain-Barré syndrome–Where do we stand?. Journal of neurology. 2009 Jan 1;256(1):3-12.
11. Wang Y, Sun S, Zhu J, Cui L, Zhang HL. Biomarkers of Guillain-Barre syndrome: some recent progress, more still to be explored. Mediators of inflammation. 2015;2015.
12. Cornblath DR, Mellits ED, Griffin JW, McKhann GM, Albers JW, Miller RG, Feasby TE, Quaskey SA, Guillain Barré Syndrome Study Group. Motor conduction studies in Guillain Barré syndrome: description and prognostic value. Annals of neurology. 1988 Apr;23(4):354-9.

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Association of Plasma Brain Natriuretic Peptide with Severity of Acute Ischemic Stroke

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Abstract:

Background: *Stroke is responsible for the highest mortality and disability among adult population in Bangladesh. With a death rate of 125.6 per 100,000 populations, Bangladesh ranks 34th globally for stroke related death. This study was aimed to find out association of plasma BNP with acute ischemic stroke severity which may help in management of these patients.* ***Methods:*** *This cross-sectional study was conducted in the Department of Neurology, BSMMU, Dhaka from June 2018 to October 2019. Total 45 subjects with history within 7 days and confirmed by CT scan of head or MRI of brain were selected purposively from the Neurology departments of BSMMU, NINS&H and Internal Medicine department of DMCH, Dhaka, Bangladesh. Venous blood samples were collected from these patients and analyzed at the Department of Biochemistry and Molecular Biology, BSMMU, Dhaka for estimation of plasma BNP.* ***Results:*** *This study found increased plasma BNP of >100 pg/ml in 31.1 % of acute ischemic stroke patients. Mean plasma BNP level was (74.76±52.96 pg/ml) in acute ischemic stroke patient. Significant negative correlation was found between concentration of plasma BNP and time passed in days from first appearance of stroke symptoms (r = - 0.791; p < 0.001).* ***Conclusion:*** *Plasma BNP level was significantly associated with baseline severity of acute ischemic stroke.*

Key words: *Acute Ischemic Stroke, Brain Natriuretic Peptide (BNP), National Institute of Health Stroke Scale (NIHSS)*

Introduction:

Stroke is one of the major global health problems. It found that although stroke incidence, prevalence, mortality and disability-adjusted life-years declined from 1990 to 2013 and the overall stroke burden in terms of absolute number of people affected has increased across the globe in all age[1]. In 2010, stroke was the fifth leading cause of mortality in Bangladesh[2]. It is the third most common cause of death in Bangladesh[3]. However, at present, stroke is the leading cause of death in Bangladesh, followed by ischemic heart disease[4]. So, it is evident that stroke mortality is rising through the years. Stroke prevalence is 0.3% in Bangladesh and it is also the number one cause of disability in Bangladesh[3]. Inflammation and activation of the neuroendocrine systems comprise important aspects of stroke pathophysiology[5]. Activation of the sympathetic nervous system and the hypothalamic pituitary adrenal axis in acute ischemic stroke is associated with elevated levels of neuroendocrine biomarkers[6]. Several of these potential biomarkers has been tested recently to early diagnosis of ischemic stroke, predict severity and assess short- and long-term prognosis.

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Brain natriuretic peptide (BNP) is a 32 amino acid polypeptide containing a 17 amino acid ring structure that was first isolated from porcine brain in 1988[7]. Human BNP gene is located on short arm of Chromosome 1 and encodes the 108 AA pro hormone called pro-BNP[8]. Molecular Weight of glycosylated BNP precursor is 25-36 kDa, whereas, molecular Weight of mature deglycosylated BNP is12 kDa[9]. BNP denotes the biological activity of natriuresis, diuresis, vasodilatation, smooth muscle relaxation[8,11].It is secreted mainly from cardiac ventriclesand various cardiac disorders (e.g., acute coronary syndrome, left ventricular dysfunction, heart failure, atrial fibrillation) leads to increase in plasma BNP[12,13,14].Common non cardiac causes of increased BNP includes increased age, female sex, renal failure and sepsis[14,15].

Studies have shown that plasma BNP level elevated in acute ischemic stroke patients, especially in cardioembolic stroke[16,17]. However, it has been found that plasma BNP is significantly increased in acute ischemic stroke patients even without any evidence of cardiac dysfunction[18].A proposed mechanism of increased plasma BNP is reported by increased catecholamine[19,20]. National institute of Health Stroke Scale (NIHSS), the clinical tool to measure stroke severity has some limitations. Because, it needs training for assessment and inconsistency found in measurement among different clinicians[6]. Again, study have shown, lower NIHSS scores in right hemispheric syndromes than left hemispheric syndromes and less reliable severity scores in posterior circulation syndromes compared to anterior circulation syndromes[6]. Therefore, it is time demanding to identify a biomarker for correct and unbiased assessment of severity in acute ischemic stroke patients, which may substitute or compliment NIHSS. These evidences and justifications led us to formulate hypothesis that plasma BNP may be associated with severity of acute ischemic stroke.

Methods:

This was designed as analytic cross-sectional study. This study was carried out from June, 2018 to October, 2019 from indoor and outdoor services of Bangabandhu Sheikh Mujib Medical University (BSMMU), National Institute of Neurosciences & Hospital (NINS&H) and Dhaka Medical College Hospital (DMCH), Dhaka Bangladesh. The laboratory work (measurement of plasma brain natriuretic peptide) was performed in the department of "Biochemistry and Molecular biology" of BSMMU. Forty-five acute ischemic stroke patients with history within 7 days who were admitted in the Neurology department of BSMMU, NINS&H, Dhaka and Internal Medicine department of DMCH, Dhaka or patients who attended outpatient departments within this period were selected as study population for this study. Subjects were selected by purposive sampling method. After ethical clearance from Institutional Review Board (IRB) of BSMMU, forty-five patients between 18 to 75 years of age of both sexes were selected. Only acute ischemic stroke presented within 7 days of symptom onset and confirmed by CT scan of Head or MRI of Brain were enrolled in this study. Patients having conditions which may affect the plasma BNP level like acute myocardial infarction, heart failure, sepsis, renal failure (s. creatinine >2.5 mg/dl), increased age (>75 years) were excluded from this study. The aims and objectives of the study were explained to the patients and/or attendants in easily understandable local language and then informed written consent was taken.

Blood samples were taken from all selected patients to measure plasma BNP. Their demographic data, examination findings including NIHSS score, laboratory findings and radiological data recorded and copies of investigation reports were preserved. All data collection sheets were filled by the researcher himself. EDTA plasma was used for the ARCHITECT BNP assay. Three milliliters (3 ml) of venous blood samples, preferably from median cubital vein, were collected from each patient in plastic made blood collecting (purple head) tubes by the researcher, because the BNP molecule has been shown to be unstable in glass containers. The ARCHITECT BNP assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of human B type natriuretic peptide (BNP) in human EDTA

plasma on the ARCHITECT iSystem was used for this estimation. The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is a direct relationship between the amount of BNP in the sample and the RLUs detected by the ARCHITECT iSystem optics. Continuous variables were expressed as Mean ± SD. Categorical variable were presented by frequency, percentage and graph. Qualitative data analyzed by chi square test. Quantitative variables were analyzed by student's t test. The correlations between plasma BNP and the other variables were calculated using spearman's correlation test. The cutoff for statistical significance was set at p <0.05 for all data analysis. Data input was done through Microsoft Office Excel version 2016 and Statistical analysis was done by using SPSS (version 22; SPSS Inc., Chicago, IL, USA).

Results:

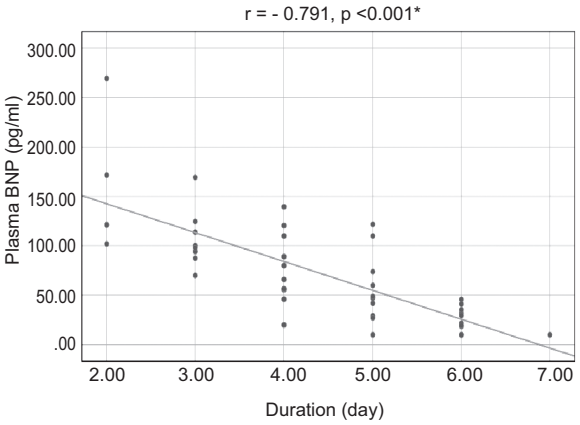
Total 45 patients of acute ischemic stroke were taken in thisstudy. Mean age was 54.04±13.17 years. Most of the subjects were between 41-60 years' age group. Male subjects were larger in proportion (60.0%) with male-female ratio of 1.5: 1.

Table-I

Distribution of plasma BNP among acute ischemic stroke patients (n=45)

BNP level (pg/ml)	Acute ischemic stroke
1-50	19(42.2%)
51-100	12(26.7%)
>100	14(31.1%)
Total	45(100.0%)
Mean±SD	74.76±52.96

Figure-1 showing, a scatter diagram and correlation of plasma BNP (pg/ml), measured from the blood sample taken during the interview, with the approximate time elapsed in days from the first appearance of the stroke symptoms among the subjects as reported by the patients or attendants. Spearman's correlation coefficient test found statistically significant (p value <0.001) negative correlation between these two variables (r = -0.791).



*significant
r= degree of correlation

Fig.-1: *Scatter diagram showing the correlation between plasma BNP and time passed (days) from appearance of first stroke symptoms (n=45)*

Figure-2 showing, frequency of different stroke syndromes according to OCSP classification. Among the acute ischemic stroke patients, Partial anterior circulation stroke and lacunar stroke was comprised 31.1% each. Total anterior circulation stroke was found in 28.9 % of patients. However, least number (8.9%) of subjects were suffering from posterior circulation stroke.

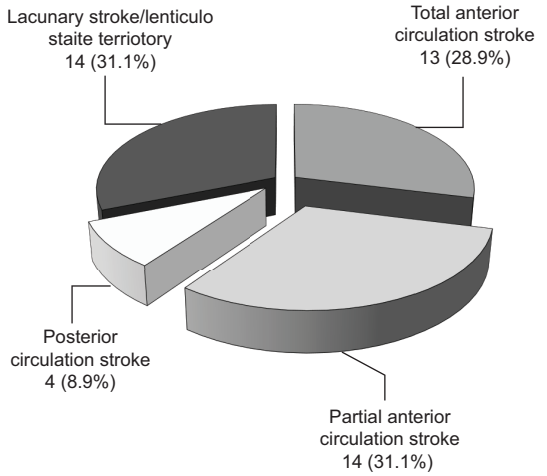
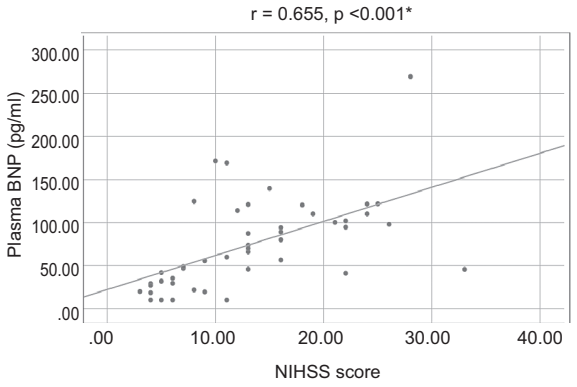


Fig.-2: *Pie chart showing frequency of ischemic stroke subtypes according to Oxfordshire community stroke project (OCSP) classification (n=45)*



*significant , r= degree of correlation

Fig.-3: *Scatter plot showing the correlation of plasma BNP with NIHSS severity score (n=45)*

Table-II

Difference of plasma BNP level inacute ischemic stroke subtypes classified by OCSP (n=45)

Stroke types	Mean±SD	p-value
Total anterior circulation stroke	111.48±54.14	0.003[s]
Partial Anterior Circulation Stroke	72.49±34.47	
Lacunar Stroke	60.04±53.88	
Posterior Circulation Stroke	14.90±5.66	

Data were analyzed by one-way ANOVA test,
s= significant

Table-III

Distribution of severity according to NIHSS score among acute ischemic stroke patients (n=45)

NIHSS	Frequency	Percent
Minor stroke(1-4)	5	11.1
Moderate stroke(5-15)	24	53.3
Moderate to severe stroke(16-20)	6	13.3
Severe stroke(>20)	10	22.2
Total	45	100.0

Table-III

Plasma BNP level in different severity categories among acute ischemic stroke patients (n=45)

Severity category (NIHSS score)	Mean±SD	p-value
Minor stroke (1-4)	20.96±7.60	0.008 [s]
Moderate stroke (5-15)	66.86±49.0	
Moderate to severe stroke (16-20)	91.70±22.54	
Severe stroke (≥21)	110.44±62.42	

Data were analyzed by one-way ANOVA test,
s= significant

Discussion:

This study was conducted with an aim to find out association between plasma BNP andseverity of acute ischemic stroke. In this cross-sectional study, total 45 acute ischemic stroke patients were enrolled. The study subjects were taken from BSMMU, NINS&H, DMCH, Dhaka, Bangladesh. Any relation of plasma BNP with NIHSS score of clinical severity was evaluated through this study, along with the variation of plasma BNP level in different areas of brain involvement according to Oxfordshire Community Stroke Project (OCSP) classification. Study was conducted from June, 2018 to October, 2019. Analysis of age distribution of the study population showed that mean age (±SD) was 54.04(±13.17) years in acute ischemic stroke patients. Male outnumber female in ischemic strokepatients (male: female =1.5:1). Most of the study subjects were middle aged adults of 41-60 years.Increased plasma BNP level above 100pg/ml was found in 31.1% of acute ischemic patients. This finding is consistent with another study which found elevated plasma BNP in 44% subjects of acute ischemic stroke[22]. Significantly increased mean BNP value of (74.76±52.96 pg/ml)was observed in the acute ischemic stroke patients. Similarly, high mean BNP was reported in earlier studies in acute ischemic stroke patients[18,23].The mean BNP was found much higher in earlier studies than found in the current study[18,23]. The higher mean plasma BNP in the above-mentioned studies may be due to early access of patient to health care services in those studies where

sampling of blood was possible without any delay from onset of stroke symptoms[18]. Another possibility of high mean plasma BNP in the above-mentioned studies may be due to inclusion of all subjects irrespective of their cardiac and renal function status.

In this study, a decreasing trendof plasma BNP level observed in ischemic stroke patients as the time increases from onset of stroke symptoms to collection of blood for BNP estimation. Significant negative correlation found between plasma BNP level and time passed in days from stroke ($r = -.791$; $p < 0.001$). Similar dynamic decrease of natriuretic peptide with time from day "0" to day "6" after stroke reported previously[24,25]. This study found statistically significant positive correlation ($r = .655$; $p < 0.001$) between plasma BNP and severity of stroke measured by National institute of health stroke scale, through Spearman's correlation test. This correlation was also observed by in study done on hospital-based stroke patients in Italy[26]. Current study showed that as severity increased, mean plasma BNP rise significantly from 'minor stroke' (20.96 pg/ml) to 'moderate stroke' (66.86 pg/ml). Further increase of plasma BNP also found in 'moderate to severe stroke' (91.70 pg/ml) and 'severe stroke' (110.44 pg/ml). Finding in this study is consistent with previous studies where BNP level was reported independently associated with clinical severity[27]. Although, association between infarct volume (measured in DWI sequence of MRI) and plasma BNP among ischemic stroke patients was found previously, it was not evaluated in this current study[27]. In this study, a statistically significant difference observed in plasma BNP level depending on anatomical variation of infarct as classified by Oxfordshire community stroke project (OCSP). Plasma BNP concentration was found highest (111.48 pg/ml) among 'total anterior circulation infarct' and least (14.90 pg/ml) in 'posterior circulation infarct'. Plasma BNP measurements were in between of the above values for 'partial anterior circulation infarct' (72.49 pg/ml) and 'lacunar infarct' (60.04 pg/ml). These finding accords with earlier studies which have shown highest mean BNP value among the patients of total anterior circulation infarct[23]. The large rise of BNP in anterior circulation infarcts could be due to larger area of involvement through involvement of carotid circulation.

The association, we found, between plasma BNP level with acute ischemic stroke severity could strengthen the potential role of BNP for assessment of severity in acute ischemic stroke both in terms of speed and ease. It may also help to anticipate infarct site.

Conclusion:

This study reveals that high plasma brain natriuretic peptide is associated with clinical severity in acute ischemic stroke. So, plasma brain natriuretic peptide could be a marker for estimation of severity in these patients. Likewise, plasma BNP is associated with anatomical location of ischemic stroke with high level in anterior circulation strokes. This will help to identify infarct site of acute ischemic stroke according to Oxfordshire community stroke project classification. Current study also reveals that Plasma BNP level is significantly higher in acute ischemic stroke and blood level of BNP falls gradually with time after the ischemic stroke.

References:

1. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. Circulation research. 2017 Feb 3;120(3):439-48.
2. Centers for Disease Control and Prevention (CDC. Prevalence of stroke—United States, 2006-2010. MMWR. Morbidity and mortality weekly report. 2012 May 25;61(20):379.
3. Islam MN, Moniruzzaman M, Khalil MI, Basri R, Alam MK, Loo KW, Gan SH. Burden of stroke in Bangladesh. International journal of stroke. 2013 Apr;8(3):211-3.
4. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, Casey DC, Charlson FJ, Chen AZ, Coates MM, Coggeshall M. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. The lancet. 2016 Oct 8;388(10053):1459-544.

5. Elkind MS. Inflammation, atherosclerosis, and stroke. The neurologist. 2006 May 1;12(3):140-8.

6. Tu WJ, Dong X, Zhao SJ, Yang DG, Chen H. Prognostic value of plasma neuroendocrine biomarkers in patients with acute ischaemic stroke. Journal of neuroendocrinology. 2013 Sep;25(9):771-8.

7. Sudoh T, Minamino N, Kangawa K, Matsuo H. Brain natriuretic peptide-32: N-terminal six amino acid extended form of brain natriuretic peptide identified in porcine brain. Biochemical and biophysical research communications. 1988 Sep 15;155(2): 726-32.

8. Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM. Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. IncGMP: Generators, Effectors and Therapeutic Implications 2009 (pp. 341-366). Springer, Berlin, Heidelberg.

9. Katoh C, Osanai T, Tomita H, Okumura K. Brain natriuretic peptide is released from human astrocytoma cell line U373MG under hypoxia: a possible role in anti-apoptosis. Journal of endocrinology. 2011 Jan 1;208(1):51.

10. Hall C. Essential biochemistry and physiology of (NT pro) BNP. European journal of heart failure. 2004 Mar;6(3):257-60.

11. Nishikimi T, Kuwahara K, Nakao K. Current biochemistry, molecular biology, and clinical relevance of natriuretic peptides. Journal of cardiology. 2011 Mar 1;57(2):131-40.

12. Marshall WJ, Lapsley M, Day A, Ayling R. Clinical Biochemistry E-Book: With Expert Consult access. Elsevier Health Sciences; 2014 Mar 5.

13. Wang TJ, Larson MG, Levy D, Leip EP, Benjamin EJ, Wilson PW, Sutherland P, Omland T, Vasan RS. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. The American journal of cardiology. 2002 Aug 1;90(3):254-8.

14. Yang J, Zhong C, Wang A, Xu T, Bu X, Peng Y, Wang J, Peng H, Li Q, Ju Z, Geng D. Association between increased N-terminal pro-brain natriuretic peptide level and poor clinical outcomes after acute ischemic stroke. Journal of the neurological sciences. 2017 Dec 15;383:5-10.

15. Cowie MR, Jourdain P, Maisel A, Dahlstrom U, Follath F, Isnard R, Luchner A, McDonagh T, Mair J, Nieminen M, Francis G. Clinical applications of B-type natriuretic peptide (BNP) testing. European heart journal. 2003 Oct 1;24(19):1710-8.

16. Nakagawa K, Yamaguchi T, Seida M, Yamada S, Imae S, Tanaka Y, Yamamoto K, Ohno K. Plasma concentrations of brain natriuretic peptide in patients with acute ischemic stroke. Cerebrovascular Diseases. 2005;19(3):157-64.

17. Makikallio AM, Makikallio TH, Korpelainen JT, Vuolteenaho O, Tapanainen JM, Ylitalo K, Sotaniemi KA, Huikuri HV, Myllyla VV. Natriuretic peptides and mortality after stroke. Stroke. 2005 May 1;36(5):1016-20.

18. Sayan S, Kotan D. Levels of brain natriuretic peptide as a marker for the diagnosis and prognosis of acute ischemic stroke. Archives of medical sciences. Atherosclerotic diseases. 2016;1(1):e16.

19. Naveen V, Vengamma B, Mohan A, Vanajakshamma V. N-terminal pro-brain natriuretic peptide levels and short term prognosis in acute ischemic stroke. Annals of Indian Academy of Neurology. 2015 Oct;18(4):435.

20. Iltumur K, Karabulut A, Apak I, Aluclu U, Ariturk Z, Toprak N. Elevated plasma N-terminal pro–brain natriuretic peptide levels in acute ischemic stroke. American heart journal. 2006 May 1;151(5):1115-22.

21. Bambrick L, Kristian T, Fiskum G. Astrocyte mitochondrial mechanisms of ischemic brain injury and neuroprotection. Neurochemical research. 2004 Mar 1;29(3):601-8.

22. Chaudhuri JR, Sharma VK, Mridula KR, Balaraju B, Bandaru VC. Association of plasma brain natriuretic peptide levels in acute ischemic stroke subtypes and outcome. Journal of Stroke and Cerebrovascular Diseases. 2015 Feb 1;24(2):485-91.

23. Menon B, Ramalingam K, Conjeevaram J, Munisusmitha K. Role of brain natriuretic peptide as a novel prognostic biomarker in acute ischemic stroke. Annals of Indian Academy of Neurology. 2016 Oct;19(4):462.

24. Giannakoulas G, Hatzitolios A, Karvounis H, Koliakos G, Charitandi A, Dimitroulas T, Savopoulos C, Tsirogianni E, Louridas G. N-terminal pro-brain natriuretic peptide levels are elevated in patients with acute ischemic stroke. Angiology. 2005 Nov;56(6):723-30.

25. Fonseca AC, Matias JS, e Melo TP, Pires C, Geraldes R, Canhão P, Brito D, Ferro JM. Time course of NT pro BNP levels after acute ischemic stroke. Acta Neurologica-Scandinavica. 2013 Oct;128(4):235-40.

26. Barbieri A, Giuliani E, Carone C, Pederzoli F, Mascheroni G, Greco G, Stucchi C, Genedani S. Clinical severity of ischemic stroke and neural damage biomarkers in the acute setting: theSTROkeMArkers (STROMA) study.

27. Tomita H, Metoki N, Saitoh G, Ashitate T, Echizen T, Katoh C, Fukuda M, Yasujima M, Osanai T, Okumura K. Elevated plasma brain natriuretic peptide levels independent of heart disease in acute ischemic stroke: correlation with stroke severity. Hypertension Research. 2008 Sep; 31(9):1695.

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Association of Hypertension with Body Mass Index

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Abstract:

Background: *Body mass index (BMI) is positively associated with blood pressure (BP). Weight loss significantly reduces blood pressure (BP).The principal aim was to find out the association of Body Mass Index (BMI) with hypertension.* ***Methods:*** *This cross-sectional study was conducted at outpatient department of Bangabandhu Sheikh Mujib Medical University (BSMMU). A total of 1128 hypertensive patients were included in this study by purposive sampling method. Staging of hypertension was done according to The JNC 7 Hypertension Guidelines. BMI was calculated by measuring weight in kilograms divided by height in meters squared.* ***Results:*** *This study demonstrated that majority (58.1%) were within 40 to 60 years. 63.7% patients were male and 36.3% were female. Maximum observed systolic blood pressure was 170 mm of Hg and minimum 110 mm of Hg. Maximum diastolic blood pressure was 120 mm of Hg and minimum 60 mm of Hg. Out of 1128 hypertensive patients' 21% patients had normal BMI, 66.7% overweight, 8.8% obese and 3.5% patients were under weight. So hypertension was found more in overweight study subjects which was found statistically significant.* ***Conclusion:*** *The prevalence of hypertension is more in increased BMI.*

Keywords: *Hypertension, Body weight, BMI etc.*

Introduction:

Body mass index (BMI) is positively associated with blood pressure (BP); this association has critical implications for countries like China, where hypertension is highly prevalent and obesity is increasing[1]. Weight loss significantly reduces blood pressure (BP), suggesting that BMI is not merely a marker of factors associated with high BP but is causally associated[2-4]. Hypertension has proven to be a silent killer contributing to many deaths and considerably increasing morbidity Worldwide[5].

Hypertension is rapidly emerging as a major public health problem in developing countries[6]. 25%of world adult population is already hypertensive. Almost three quarters of the hypertensive population are in developing countries[7]. Nationwide survey on NCD conducted in Bangladesh in 2010 indicated that the prevalence of hypertension is 17.9%[8]. Twelve million people suffers from hypertension in Bangladesh[9]. So this association might help in the prevention of hypertension and thereby prevent target organ damage.

Methods:

This cross-sectional study was conducted at outpatient department of Bangabandhu Sheikh Mujib Medical University from January, 2017 to December, 2017. A total of 1128 patients were included in this study by purposive sampling method. All the patients were diagnosed cases of hypertension (BP >140/90 mm of Hg). This study included adult patient aged ≥18 years. Blood pressure was measured with a well-calibrated sphygmomanometer.

Staging of hypertension was done according to The Seventh Report of the Joint National Committee on Prevention, detection, Evaluation and treatment of High Blood Pressure. Body mass index (BMI) of all hypertensive patients was then calculated as weight in kilograms divided by height in meters squared. In addition to physical measurements,

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socio-demographic data and data on basic medical history were collected from standardized in-person interviews by trained medical staff.

Results:

This study intended to find the association between hypertension and BMI. The findings derived from data analyses were presented below.

In this study, out of 1128 hypertensive patients majority 655 (58.1%) were between 40-60 year of age and about 718 (63.7%) were male and 410 (36.3%) were female with significant association (p<001). (Table-I).

Socio-demographic data demonstrated that educational status of the study subjects included majority 314 (27.8%) were graduate with significant association (p<0.001) and Occupation comprised majority were Service holder 548 (48.6%) with significant association (p<0.001).Most 733 (65%) patients were from rural areas and the rest (35%) was from urban areas with significant association (p<0.001). Majority of the study patients 851(75.4%) had no family history of hypertension with insignificant association (p=0.63).(Table-II).

Our analysis includes 1128 participants all were hypertensive. Among the study subjects, 715 participants (66.7%) were overweight (BMI 25.0-29.9) with significant association (p=0.002), and 128 participants (10.3%) were obese (BMIe"30) with significant association (p<0.001), as defined by the World Health Organization international classification[15,10]. Majority 715 (66.7%) patients were overweight. (Table-III).

Table-I

Distribution of age and sex of the study subjects (n = 1128)

Age (years)	Sex		Total
	Male	Female	
18-40	315 (27.92%)	140 (12.41%)	455 (40.3%)
40-60	385 (34.13%)	270 (23.93%)	655 (58.1%)
> 60	18 (1.6%)	00 (00%)	18 (1.6%)
Total	718 (63.7%)	410 (36.3%)	1128 (100%)

Table-II

Socio-demographic characteristics of the study subjects (n = 1128)

Variables		Sex		Total
		Male	Female	
Educational	Primary	207	63	270 (23.9%)
Qualification	Secondary	87	175	262 (23.2%)
	Higher Secondary	81	24	105 (9.3%)
	Graduate	286	28	314 (27.8%)
	Postgraduate	57	120	177 (15.7%)
Total		718	410	1128 (100%)
Occupation	Farmer	138	00	138 (12.2%)
	Service	428	120	548 (48.6%)
	Businessman	152	00	152 (13.5%)
	Others	00	290	290 (25.7%)
Total		718	410	1128 (100%)
Residence	Rural	195	200	395 (35%)
	Urban	523	210	733 (65%)
Total		718	410	1128 (100%)
Family history	Yes	100	53	153 (13.56%)
HTN	No	618	357	975 (86.44%)
Total	718	410	1128 (100%)	

Table-III

BMI of the study subjects (n = 1128)

Variables		Sex		Total
		Male	Female	
BMI	Normal	163	73	236 (20%)
	Overweight	466	249	715 (66.7%)
	Obese	48	80	128 (10.3%)
	Under weight	41	08	49 (3.5%)
Total		718	410	1128 (100%)

Discussion:

This study describes the association between BMI and BP which was conducted in tertiary care hospital of Bangladesh. In this study among 1128 hypertensive patients majority (58.1%) were 40 to 60 years of age and 63.7% were male and 36.3% female with Male female ratio 1.75:1.

Hypertension is more common in men than in women of same age. Sex difference in the prevalence of hypertension may be mainly attributed to the differences in dietary habit, life style choice, salt intake, Physical activity level and some genetic polymorphism[11].

Among 1128 hypertensive patients only 13.56% patients had positive family history and majority (75.4%) patients had no family history of hypertension. Positive family history is associated with hypertension prevalence double that found in patients with negative history and is independent with weight. When over weight is also present, however hypertension prevalence is three to four times as high[12].

BMI status of the study subjects found that majority 66.7% were overweight. The findings of this study is consistent with a study conducted in china, which also showed that the association of BMI with SBP and DBP was consistently positive across 86 subgroups defined by socio-demographic variables and was nearly linear, with little variation in its shape[1].

Conclusion:

The prevalence of hypertension is more in increased BMI. The limitation of the present study is data were collected from single center. Further multi-center study was recommended to validate the finding of the present study.

References:

1. George C. Linderman, BS; Jiapeng Lu, PhD; Yuan Lu, ScD; Xin Sun, MS; Wei Xu, MS; et al. JAMA Network Open.2018; 1(4):e181271. doi:10.1001/jamanetworkopen.2018.71.
2. Rahmouni K, Correia ML, Haynes WG, Mark AL. Obesity-associated hypertension: new insights into mechanisms. Hypertension. 2005; 45(1):9-14. doi:10.1161/01.HYP. 0000 151325.83008.b4
3. Rahmouni K. Obesity-associated hypertension: recent progress in deciphering the patho-genesis. Hypertension.2014;64(2):215-221. doi:10.1161/HYPER TENSIONAHA.114. 00920
4. Sowers JR. Obesity as a cardiovascular risk factor.Am J Med. 2003; 115(suppl 8A):37S-41S. doi:10.1016/j.amjmed.2003.08.012
5. Kotchen TA, Hypertensive Vascular Disease; In: Longo DL, Fauci SA, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine ,18th edition. New York: McGrawHill publishers, 2012. Volll; 2042-59.
6. Hypertension Study Group. Prevalence, awareness, treatment and control of hypertension among the elderly in Bangladesh and India: A multicentre study. Bull World Health Organ. 2001; 79:490–500.
7. Kearny PM, Global burden of Hypertension: analysis of worldwide data. *Lancet 2005*; 365:217-23.

8. Rahman M, Chowdhury MAJ etal.NCD Risk Factor Survey. BSM 2010; 1- 35.

9. Sultana M H. Non-adherence to drug treatment in patients of essential hypertension. BMRC Bull; 2009; 35: 76-78.

10. Consultation WHOE; WHO Expert Consultation. Appropriate body-mass index for Asian populations and itsimplications for policy and intervention strategies.Lancet. 2004; 363(9403):157-163. doi:10.1016/S0140-6736(03)15268-3

11. Ruixin Y, Jinzhen W, Shangling P, Weixiong L, Dezhai Y, Yuming C. Sex differences in environmental and genetic factors for hypertension. The American journal of medicine 2008;121(9):811-819.

12. Stamler R, Stamler J, Reidlinger WF, Algera G, Roberts RH. Family (Parentaral) history and prevalence of hypertension. JAMA 1979;241(1):43-46.

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REVIEW ARTICLE

Functional Neuroimaging: Single Photon Emission Computed Tomography (SPECT) In Neurological Disorders

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Abstract:

A single photon emission computed tomography (SPECT) scan is a functional nuclear imaging technique performed to evaluate regional cerebral perfusion. Because cerebral blood flow is closely linked to neuronal activity, the activity distribution is presumed to reflect neuronal activity levels in several areas of the brain. Although structural magnetic resonance imaging (MRI) and computed tomography (CT) provide exquisite anatomical detail, SPECT provide complementary functional information. Frequently, brain pathology will manifest as functional changes before anatomical changes are detectable. SPECT has clinical value in the diagnosis, therapeutic management, and follow-up of patients. A general consideration of the clinical value of this technique is followed by relevant information on cerebral physiology and pathology for proper understanding of brain SPECT images. The diversity of central nervous system diseases and therefore the still incomplete knowledge of the mechanisms that underlie them have contributed to the success of brain perfusion SPECT as a research tool in neurosciences. Finally, step-by-step recommendations for interpreting and reporting brain perfusion SPECT images are provided to get the utmost clinical beneût from this technique.

Key Words: *SPECT; Regional cerebral blood ûow; Functional Neuroimaging*

Introduction:

Neuroimaging is an emergent method of investigation that deals with the in vivo depiction of anatomy and function of the central nervous system (CNS) in health and disease[1].It classifies into two broad categories: structural imaging and functional imaging. Structural imaging such as CT or MRI, which deals with the structure of the brain and the diagnosis of large-scale intracranial diseases (such as a tumor, infection etc.), as well as injury. Functional imaging such as SPECT or PET, which is used to diagnose metabolic diseases and lesions on a finer scale (such as dementia, PD etc), and also for neurological and cognitive-psychology research.[2] Functional imaging allows the brain's information processing to be visualized directly, because activity in the involved area of the brain increases metabolism and "lights up" on the scan.

Brain SPECT provides tridimensional information on the perfusion and metabolic status of brain tissue. This information is often complementary to the anatomic detail provided by structural

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neuroimaging techniques .This tomographic imaging technique is using gamma ray which is very similar to conventional nuclear medicine planar imaging employing a gamma camera but is in a position to supply true 3D information. It evaluates regional cerebral perfusion because cerebral blood flow is closely linked to neuronal activity, the activity distribution is presumed to reflect neuronal activity levels in different areas of the brain. A 3-dimensional representation of cerebral blood flow can be literated using gamma detectors, allowing for interpretation.

Radioisotopes in SPECT:

The radioisotopes typically utilized in SPECT to label tracers are iodine-123, technetium-99m, xenon-133, thallium-201, and fluorine-18. Among them lipophilic, PH-neutral three radioisotopes have approved by the U.S. Food and Drug Administration (FDA) for clinical use in brain perfusion[3,4]. The oldest one, iodine 123 isopropyliodoamphetamine (IMP), distributes proportionally to rCBF over a range of flows but may be decreased with low plasma pH as in cerebral ischemia or acidosis. Brain activity remains relatively constant from 20 to at least 60 minutes after injection which is widely used in Japan, not commercially available in the United States. Technetium-99m hexamethyl propyleneamine oxime (HMPAO), a lipid-soluble macrocyclic amine, is available for routine clinical use [6]. Brain uptake is rapid and reaches its maximum within 10 minutes. Radiotracer distribution remains constant for many hours after injection. A third radiopharmaceutical, 99mTc ethyl cysteinate dimer (ECD) has a rapid blood clearance, resulting in high brain-to-soft tissue activity ratios early and with less exposure to radiation[5]. The Tc-radiolabeled compounds are stable for about 6 hours, facilitating their use for the study of episodic phenomena, such as seizures. The inert gas xenon-133(133Xe) has also been used to study rCBF. 133Xe SPECT is performed after inhalation of the gas and is based on clearance techniques that relate the change in radiotracer activity over time to blood flow[5]. The principal advantage over other tracers that remain in the brain is that rCBF can be measured quantitatively and repeatedly without arterial sampling. 133Xe does have major limitations, including poor spatial resolution and the need for specialized instrumentation. Various drugs and other chemicals can be labeled with these isotopes too that enhance regional cerebral blood flow, such as acetazolamide. Acetazolamide increases local pCO2 and causes arteriolar dilation, allowing for assessment of cerebrovascular reserve in transient ischemic attack (TIA), stroke and vascular anomalies and distinguishing vascular from neuronal causes of dementia[6].

Principles of SPECT:

SPECT integrates computed tomography (CT) and a radioactive tracer. The radioisotopes usually used in SPECT to label tracers are iodine-123, technetium-99m, xenon-133, thallium-201, and fluorine-18. These radioactive forms of natural elements will pass through the body and be detected by the scanner. Various drugs and other chemicals can be labeled with these isotopes too. Before the SPECT scan, a tracer is injected into bloodstream. The tracer is radiolabeled, meaning it emits gamma rays that can be detected by the CT scanner. The computer collects the information emitted by the gamma rays and displays it on the CT cross-sections. SPECT imaging is performed by using a gamma camera to acquire multiple 2-D images (also called projections), from multiple angles. A computer is then used to apply a tomographic reconstruction algorithm to the multiple projections, yielding a 3-D data set and form a 3D image of brain.

The type of tracer used depends on the physicians according to the expected pathological lesions. For example, in case of suspected tumor, the radiolabled glucose (FDG) can be used to detect the metabolism of the tumor. Depending on the type of imaging system and tracer used, the resolution ranges from 14–17 mm full width at half maximum (FWHM) for single-head gamma cameras, now seldom used for brain imaging, to 8–10 mm FWHM for three- and four head camera systems and to 7–8 mm FWHM for special purpose ring-type imaging systems. In general, system cost is directly proportional to the number and

complexity of camera heads or crystals. To acquire SPECT images, the gamma camera is rotated around the patient. Projections are acquired at defined points during the rotation, typically every 3–6 degrees. In most cases, a full 360-degree rotation is used to obtain an optimal reconstruction. The time taken to obtain each projection is also variable, but 15–20 seconds is typical. This gives a total scan time of 15–20 minutes. Multi-headed gamma cameras can accelerate acquisition. For example, a dual-headed camera can be used with heads spaced 180 degrees apart, allowing two projections to be acquired simultaneously, with each head requiring 180 degrees of rotation. Triple-head cameras with 120-degree spacing are also used.

Clinical applications of SPECT:

A SPECT scan is primarily used to view how blood flows through arteries and veins in the brain. Tests have shown that it might be more sensitive to brain injury than either MRI or CT scanning because it can detect reduced blood flow to injured sites. SPECT scanning is useful for blood deprived (ischemic) areas of brain following a stroke , aid in the diagnosis and differential diagnoses of suspected dementia, assessment of brain death, mood disorders and evaluating & sub typing attention-deficit disorder. SPECT scanning is also useful for presurgical evaluation of medically uncontrolled seizures (Fig.1)[6,7]. The test can be performed between seizures (interictal) or during a seizure (ictal) to determine blood flow to areas where the seizures originate[8]. This type of scanning is also important in diagnosing stress fractures in the spine (spondylolysis), tumors and substance abuse. More recent studies have shown the accuracy of SPECT in Alzheimer's diagnosis may be as high as 88%[9]. In meta analysis, SPECT was superior to clinical exam and clinical criteria (91% vs. 70%) in being able to differentiate Alzheimer's disease from vascular dementias[10]. This latter ability relates to SPECT's imaging of local metabolism of the brain, in which the patchy loss of cortical metabolism seen in multiple strokes differs clearly from the more even or "smooths" loss of non-occipital cortical brain function typical of Alzheimer's disease (Fig. 2). Another recent review article showed that multi-headed SPECT cameras with quantitative analysis result in an overall sensitivity of 84-89% and an overall specificity of 83-89% in cross sectional studies and sensitivity of 82-96% and specificity of 83-89% for longitudinal studies of dementia[11].

Limitations of SPECT:

The major limitation of brain SPECT study is the attenuation by the skull. The commonly used Chang method of attenuation correction is based on a simple mathematical formula, which is susceptible to technical variation. In diagnosis of dementia with SPECT, it can be difficult to separate the real defect from the attenuation artifact.[9] Variation between images owing to the Chang attenuation correction may generate artifact when ictal-interictal subtraction SPECT scans are used for seizure localization. SPECT/CT will provide more accurate attenuation correction and diagnostic results. SPECT is technically less sophisticated and demanding when compared with positron emission tomography (PET), but provides lower-resolution images. It can be used to evaluate regional variations in blood flow, but its role in everyday clinical practice is, like that of PET, a small one.

Comparison SPECT with PET scan:

SPECT is similar to PET in its use of radioactive tracer material and detection of gamma rays. In contrast with PET, the tracers used in SPECT emit gamma radiation that is measured directly, whereas PET tracers emit positrons that annihilate with electrons up to a few millimeters away, causing two gamma photons to be emitted in opposite directions. A PET scanner detects these emissions "coincident" in time, which provides more radiation event localization information and, thus, higher spatial resolution images than SPECT (which has about 1 cm resolution). SPECT scans are significantly less expensive than PET scans, in part because they are able to use longer-lived and more easily obtained radioisotopes than PET. The test differs from a PET scan in that the tracer stays in

the blood stream rather than being absorbed by surrounding tissues, thereby limiting the images to areas where blood flows. SPECT scans are cheaper and more readily available than higher resolution PET scans.

Interpreting and Reporting Images of SPECT:
Perfusion patterns may differ from one subject to another, because the normal brain is not always completely symmetric, and small structural differences are frequent within normal subjects. This result is partly caused by variations in functional activity and therefore by a varying vascular supply to cerebral regions at the time of injection. In a normal brain perfusion SPECT image [12] regions with higher perfusion, such as cortical and subcortical gray matter structures, have the highest tracer uptake. Subcortical white matter shows low tracer uptake, and no tracer uptake is seen in areas containing cerebrospinal ûuid (i.e., cerebral ventricles, ûssures and sulcus) or bone (i.e., scalp or petrous part of temporal bones). The cerebral region showing the maximum tracer uptake varies with the radiopharmaceutical used (i.e., most probably the cerebellum with HMPAO, but the calcarine cortex with ECD), the patient's condition at the time of injection (e.g., inûuence of visual activity on calcarine cortex uptake), and image manipulation during reconstruction (i.e., inûuence of attenuation correction on basal ganglia activity). The common causes of different tracer uptake patterns in brain perfusion SPECT images shown in Table: 1.

SPECT in Epilepsy:
Patients with refractory focal epilepsy, who are candidates for surgical resection of the epileptogenic focus, frequently benefit from SPECT[12,13]. MRI is also essential in the management of these patients, although not all epileptogenic foci can be accurately localised using this modality and, conversely, not all anatomical foci are the cause of a patient's seizures. So SPECT can localize the epileptogenic focus accurately which will help for neurosurgical procedure (Fig: 1 & 2).

Table-I

Common Causes of Different Tracer Uptake Patterns in Brain Perfusion SPECT Images

Tracer uptake pattern	Causes
Cold (no uptake)	Cerebrospinal ûuid
	Edema
	Necrosis
	Space-occupying lesions
	(e.g., hemorrhage, tumors,* cysts, arteriovenous malformation, postsurgery)
Hypoactive	Ischemia
(decreased	Hypometabolism (hypofunction): degeneration, deafferentation
uptake)	Atrophy
Hyperactive	Luxury perfusion
(increased uptake)	Encephalitis
	Acetazolamide-induced vasodilation
	Hyperfunction (epilepsy [ictal], neuroactivation, other causes
	of increased neuronal activity)
	Tumors*

* Tumors can produce a variety of patterns in SPECT perfusion images.
The most frequent tumors with increased tracer uptake are meningiomas.

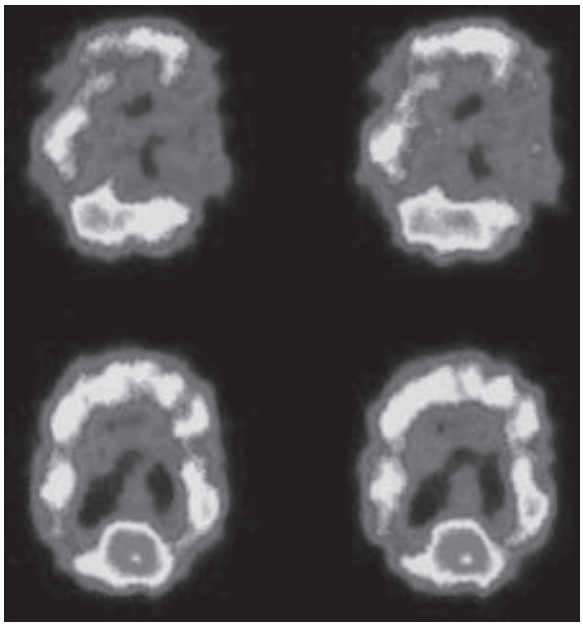


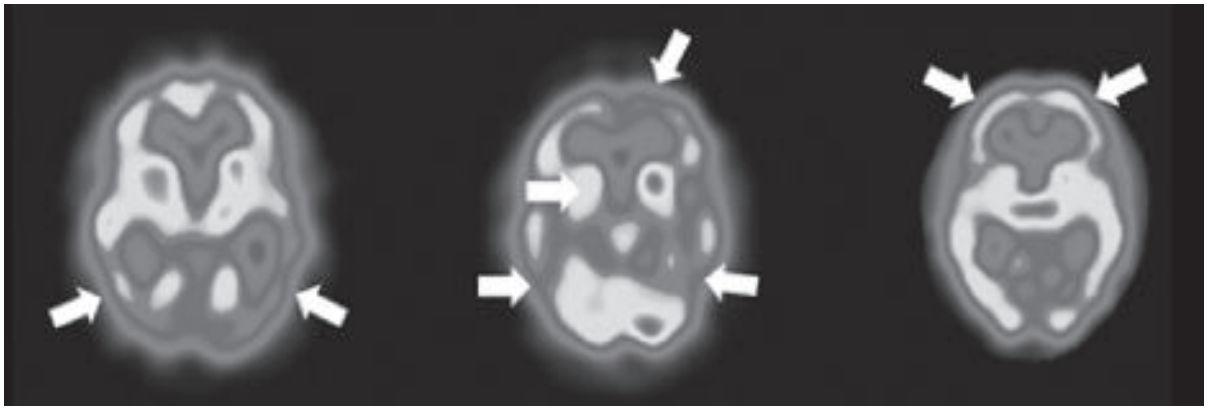
Fig.1: *A SPECT scan of a patient with uncontrolled complex partial seizures. The temporal lobe on the left side of the brain shows less blood flow than the right, confirming for the surgeon the nonfunctioning area of the brain causing seizures.Dinesh, E. et al. "Instinctive classification of Alzheimer's disease using FMRI, pet and SPECT images." 2013 7th International Conference on Intelligent Systems and Control (ISCO): 405-409.*

SPECT in Dementias:

In patients with dementia, anatomical imaging frequently shows little or no change. Characteristic patterns of functional involvement using SPECT scan, however, enable more accurate differentiation of these forms of dementia (Fig.2)[14]. In AD, reduction in regional cerebral blood flow is seen, especially in the bilateral, temporal lobes hypoperfusion (Fig.2.A). There may be also hypometabolism in the posterior parietal lobes. These changes can occur early in the disease process and may help to distinguish AD from other forms of dementia. In vascular dementia with multiple asymmetrical lesions affecting the anterior and posterior cortex and right striatum (Fig.2.B) and in fronto-temporal dementia with frontal hypoperfusion (Fig.2.C).

SPECT in Stroke:

The localization and extent of lesions as a result of defects in blood supply can be assessed by SPECT studies. This techniques are more sensitive than CT for detecting both the presence and the extent of infarction [13.15] (Fig: 3&4) .In the first 8 hr after stroke, SPECT was shown to be positive in 90%, and sensitivities of 61%–74% and specificities of 88%–98% were reported[13]. Transient ischemic attacks can be differentiated from ischemic strokes



A B C

Fig.-2: *Tc-99m HMPAO SPECT scans in 3 patients with dementia showing perfusion patterns suggestive of Alzheimer's disease, with bilateral temporo-parietal hypoperfusion (A), vascular dementia with multiple asymmetrical lesions affecting the anterior and posterior cortex and right striatum (B) and fronto-temporal dementia with frontal hypoperfusion (C).Warwick, J. "Brain imaging with SPECT and PET." Continuing Medical Education "2013; 31.8: 307-309.*

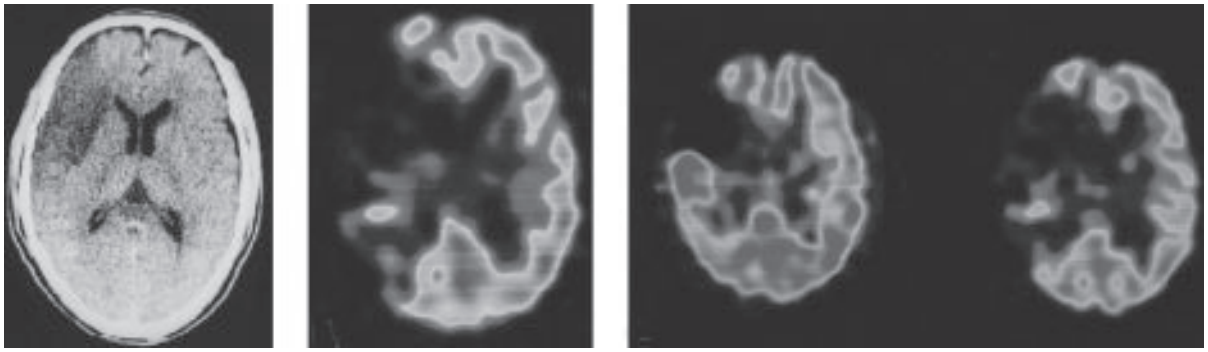


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Fig: 3: *54-year-old man with atrial fibrillation and sudden onset of left-sided hemiparesis.(A) CT scan of brain and 99mTc-HMPAO SPECT image 4.5 hours after the onset of stroke shows hypoactivity in the right frontal and temporal lobes.(B) 99mTc-HMPAO SPECT image (left) obtained 12 hours after the initial study shows hyperactivity in the right temporal lobe; a 99mTcECD SPECT image (right) shows hypoactivity in the same area.Ogasawara, K., Mizoi, K., Fujiwara, S., & Yoshimoto, T. (1999). 99mTc-bicisate and 99mTc-HMPAO SPECT imaging in early spontaneous reperfusion of cerebral embolism. AJNR., 20 4, 626-8.*

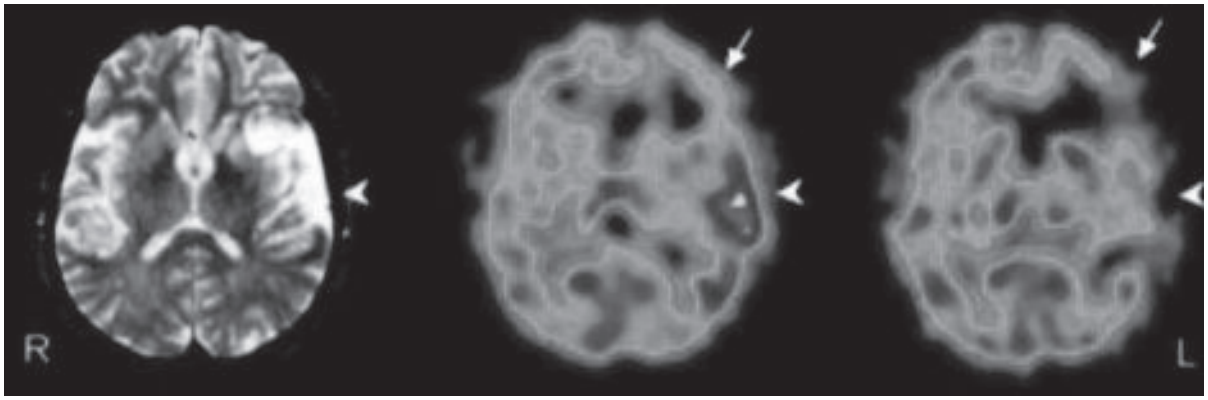

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Fig.-4: *(A) MRI (T2-weighted) at admission shows hyperintensity at site of infarction (arrowhead). (B) 99mTc-HMPAO SPECT image obtained 1 wk after stroke shows increased tracer uptake (hyperperfusion) in left temporal lobe caused by luxury perfusion (arrowhead). Hypoperfusion is also seen in left frontal cortex (arrow), intrepreted as ischemia in anatomically preserved region. (C) 99mTc-HMPAO SPECT image obtained 1 mo after stroke shows left temporal lobe hypoperfusion (arrowhead) corresponding to initial MR image of ischemia. Perfusion changes in left frontal lobe are also seen: improvement in anterior and mesial aspects caused by recovery of ischemia, as well as perfusion impairment in lateral aspect caused by extension of the infarction (arrow).Ana M. Catafau "Brain SPECT in Clinical Practice. Part I: Perfusion" J Nucl Med 2001; 42:259–271*

within 6 hr of symptom onset by, in SPECT, counting rate densities of 70% compared with the contralateral side (perfusion in stroke tissue 35%–60% of contralateral values) [16].

SPECT in Traumatic Brain Injury:

Abnormalities are more frequently found in traumatic brain injury (TBI) patients when SPECT is performed than with MRI and CT scans[17]. Hypoperfusion in the frontal and parietal lobes is common (Fig. 5), although the basal ganglia, as well as the occipital, parietal and cerebellar areas, can also be affected. SPECT has a high sensitivity and negative predictive value for TBI, and a normal study is predictive of good

recovery.[18] However, given its limited specificity, SPECT alone is not enough to diagnose TBI.

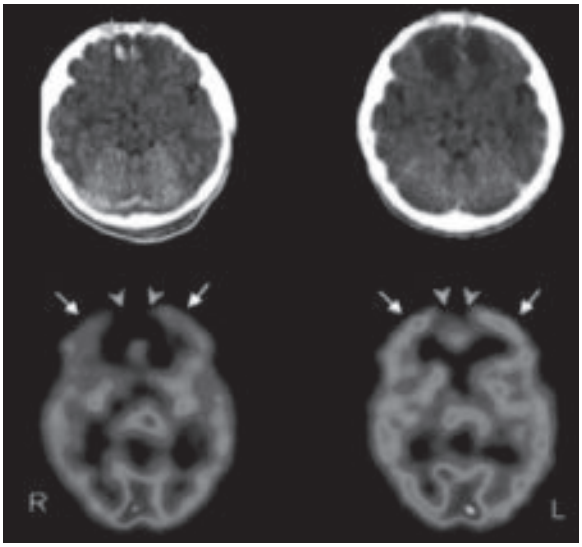


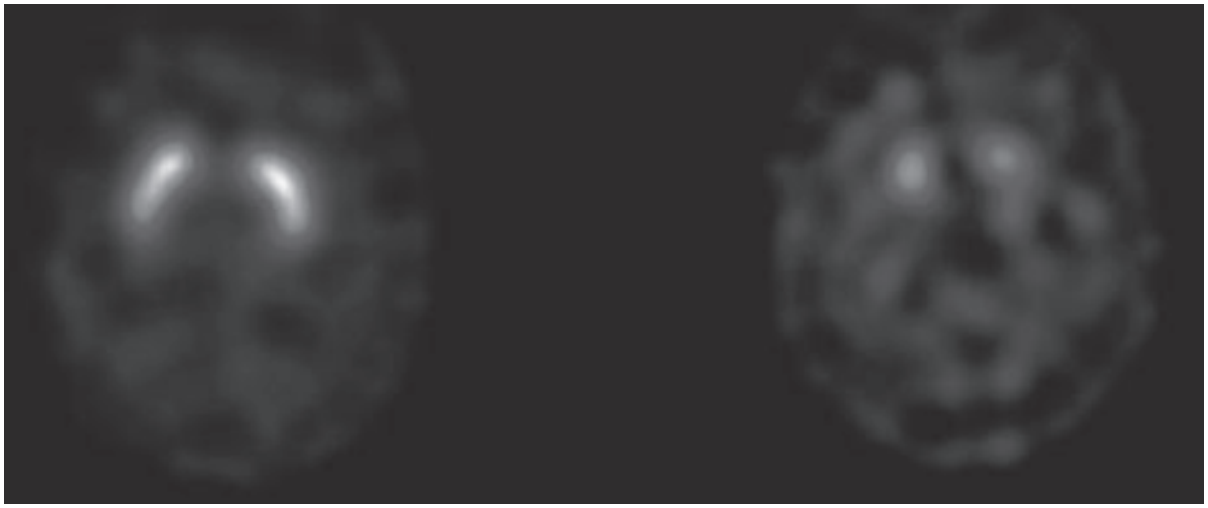
Fig.-5: *CT (top) and 99mTc-HMPAO SPECT (bottom) images from 16-y-old patient with traumatic brain injury after traffic accident. (A) CT at time of admission shows subarachnoid hemorrhage with small contusional hemorrhagic foci in both frontal lobes (orange arrowheads). SPECT was subsequently performed and shows absence of tracer uptake (cold areas) in anteromedial aspect of both frontal lobes corresponding to hemorrhagic lesions, in addition to global hypoperfusion, more marked in both frontal cortices (white arrows). (B) CT and SPECT images obtained 1 mo later at time of discharge after clinical recovery. Hypodense images in both frontal lobes can be seen on CT as consequence of hematoma's resolution. Corresponding cold areas persist on SPECT image (orange arrowheads) but show improvement in global cerebral perfusion, particularly in both frontal lobes (white arrows).Ana M. Catafau "Brain SPECT in Clinical Practice. Part I: Perfusion" J Nucl Med 2001; 42:259–271*

SPECT in Parkinsonism:

SPECT is commonly used for PD diagnosis [19]. SPECT imaging using ^{123}I-Ioflupane (^{123}I-Ioflupane-SPECT) provides information based on local binding of presynaptic dopamine transporters (DaTs) with ^{123}I-Ioflupane, which has been shown to be highly correlated with PD progression[19, 20]. This binding measure is quantitative and assesses the spatial distribution of dopamine transporters. Furthermore, ^{123}I-Ioflupane-SPECT is an imaging modality that is capable of differentiating between PD and essential tremor [21]. SPECT imaging can also distinguish between PD and drug-induced Parkinsonism[22, 23]. However, any disease that causes loss of the presynaptic dopamine neurons will appear as abnormal compared with normal controls (NCs) [24]. Thus, SPECT is not able to differentiate among PD, progressive supranuclear palsy, multiple system atrophy, and other neurodegenerative disorders that affect the dopamine neurons[25]. Most studies that use ^{123}I-Ioflupane-SPECT have focused on the striatum (i.e., putamen and caudate) [26-29]. Researchers have reported that PD has markedly reduced DaT levels in the striatum, which are correlated with disease progression and clinical scores [28,29].DaT imaging reveals reduced presynaptic neuronal degeneration in PD and other parkinsonian syndromes, even when clinical features are subtle, while conditions such as essential tremor have normal striatal DaT density[29] (Fig. 6).

SPECT in Brain tumour:

The primary role of SPECT in brain tumor patients lies on the noninvasive assessment of tumor aggressiveness, differentiation of treatment-induced necrosis from tumor recurrence, assessment of response to treatment, and estimation of overall prognosis. It also suggests that it has a high sensitivity and specificity in localizing ICSOLs and can be used in patients who cannot undergo CECT/CEMR due to contraindications or if the waiting lists for such a test is long. The common radiopharmaceuticals of SPECT are Tc-99m diethlyenetriaminepentaacetic acid (DTPA), and Tc-99m glucoheptonate (Tc-99m GHA), which are well-known renal radiopharmaceuticals, devoid of the shortcomings of Tc-99m pertechnetate. Tc-99m GHA SPECT is capable of distinguishing high-grade gliomas from low-grade gliomas as well as metastases.[30] Similarly, thallium-201, Tc-99m tetrofosmin, and Tc-99m sestamibi were found to delineate brain tumors which involved multiple mechanisms of uptake besides blood-brain barrier (BBB) disruption; however, their overwhelming cost and availability of morphological imaging techniques send these modalities to a back burner[31](Fig.7) . SPECT has also been used with the radioactive



A B

Fig.-6: *Scans of two patients with parkinsonism. In one case, DaT SPECT shows normal striatal DaT density, virtually ruling out Parkinson's disease or other causes of presynaptic dopaminergic neuron degeneration (A). The second scan shows a patient with Parkinson's disease with marked loss of striatal uptake, particularly in the putamen, and a high level of background activity (B).Warwick, J. "Brain imaging with SPECT and PET." Continuing Medical Education, 2013; 31.8:307-309.*

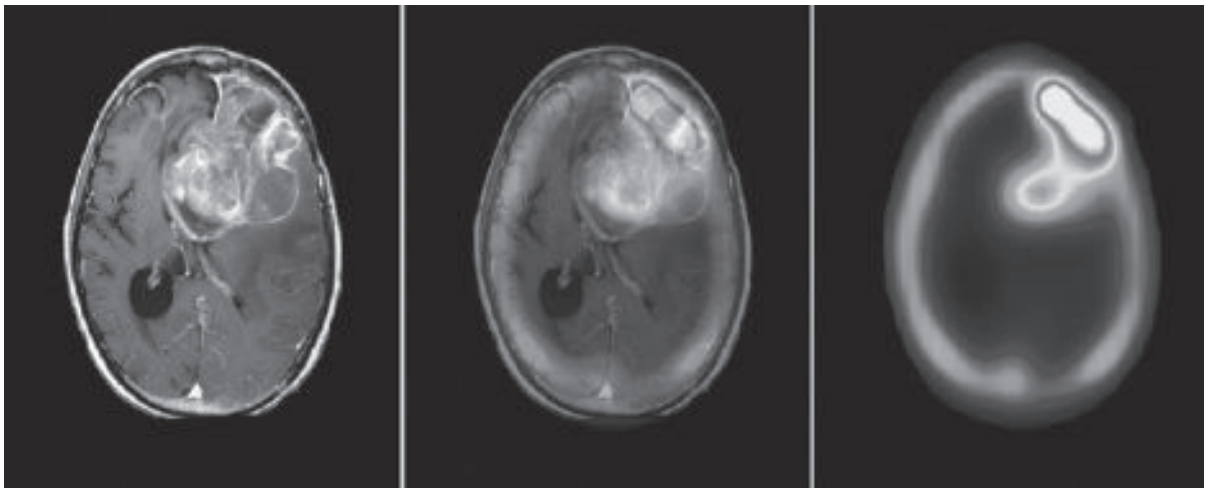


Fig.-7: *Tc-99m GHA SPECT (Tc-99m glucoheptonate) shows anaplastic oligodendroglioma of the left prefrontal region.Alam S.S, Junaid S., Ahmed S.M" Evaluation of Technetium-99m glucoheptonate single photon emission computed tomography for brain tumor grading"Asian J Neurosurg. 2016 Apr-Jun; 11(2): 118–128.*

labeled amino acid 3-(^{123}I) iodo-a-methyl-L-tyrosine for the diagnosis of brain tumors and evaluation of tumor response to radiation therapy.

Conclusion:

SPECT is rapidly emerging as an important clinical imaging method which is well-recognized clinical applications mainly in dementia, stroke, parkinsonism and epilepsy. This technique generally adds valuable information to the clinical management of patients with neurological disorders of a broad variety, helping in diagnosis, therapeutic management and follow-up. Accurate

knowledge of the physiologic and pathophysiologic basis of brain perfusion SPECT, together with the appropriate technique and careful interpretation of images and reporting, will enhance the clinical use of brain SPECT. At present, the long-term clinical and economic effects of the technology, although promising, are still to be determined.

References:

1. Filler A "The History, Development and Impact of Computed Imaging in Neurological Diagnosis and Neurosurgery: CT, MRI, and DTI"; 2009.
2. Babiloni C, Pizzella V, Gratta CD, Ferretti A, Romani GL. Fundamentals of electro-encefalography, magnetoencefalography, and functional magnetic resonance imaging. Int Rev Neurobiol. 2009; 86:67–80.
3. Juni JE, Waxman AD, Devous MD Sr, Tikofsky RS, Ichise M, Van Heertum RL, et al. Procedure guideline for brain perfusion SPECT using (99m)Tc radiopharmaceuticals 3.0. J Nucl Med Technol. 2009. 37(3):191-5.
4. Kapucu OL, Nobili F, Varrone A, Booij J, Vander Borght T, Någren K, et al. EANM procedure guideline for brain perfusion SPECT using 99mTc-labelled radio-pharmaceuticals, version 2. Eur J Nucl Med Mol Imaging. 2009;36(12):2093-102.
5. Warwick JM. Imaging of brain function using SPECT. Metab Brain Dis 2004; 19(1-2): 113-23.
6. Farid K, Petras S, Ducasse V, Chokron S, Helft G, Blacher J, et al. Brain perfusion SPECT imaging and acetazolamide challenge in vascular cognitive impairment. Nucl Med Commun. 2012; 33(6):571-80.
7. Nordberg A. Functional studies of new drugs for the treatment of Alzheimer's disease. Acta Neurol Scand. 1996; 165 (Suppl):137–44.
8. Greene JD, Miles K, Hodges JR. Neuropsychology of memory and SPECT in the diagnosis and staging of dementia of Alzheimer type. J Neurol. 1996; 243:175–90.
9. Bonte FJ, Harris TS, Hynan LS, Bigio EH, White CL. "Tc-99m HMPAO SPECT in the differential diagnosis of the dementias with histopathologic confirmation". Clin Nucl Med.2006; 31 (7): 376–8.
10. Dougall NJ, Bruggink S, Ebmeier KP. "Systematic review of the diagnostic accuracy of 99mTc-HMPAO-SPECT in dementia". Am J Geriatr Psychiatry. 2004; 12 (6): 554–70.
11. Henderson, T. "The diagnosis and evaluation of dementia and mild cognitive impairment with emphasis on SPECT perfusion neuroimaging". CNS Spectrums. 2012;17 (4): 188–89
12. Catafau AM, Lomen˜a F, Pavia J, et al. Regional cerebral blood ûow pattern in normal young and aged volunteers. A 99mTc-HMPAO SPECT study. Eur J Nucl Med. 1996;23:1329–37
13. Tamber MS, Mountz JM. Advances in the diagnosis and treatment of epilepsy. Semin Nucl Med 2012; 42:371-86.
14. Devous MD Sr, Thisted RA, Morgan GF, Leroy RF, Rowe CC. SPECT brain imaging in epilepsy: a meta-analysis. J Nucl Med. 1998; 39:285–93.
15. Henderson TA. The diagnosis and evaluation of dementia and mild cognitive impairment with emphasis on SPECT perfusion neuroimaging. CNS Spectrums 2012; 17(4):176-206.
16. Kety SS, Schmidt CF: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. Am J Physiol. 1945; 143:53–66.
17. Ingvar DH, Lassen NA. Quantitative determination of regional cerebral blood flow in man. Lancet. 1961; 278:806–807.
18. Glass HI, Harper AM. Measurement of regional blood flow in cerebral cortex of man through intact skull. Br Med J. 1963; 1:593.
19. Lin AP, Liao HJ, Merugumala SK, et al. Metabolic imaging of mild traumatic brain injury. Brain Imaging and Behavior 2012; 6:208-23.

20. Booth, T. C. et al. The role of functional dopamine-transporter SPECT imaging in parkinsonian syndromes, part 2. Am. J. Neuroradiol. 2015; 36, 236–44.

21. Shih, M. C., Hoexter, M. Q., de Andrade, L. A. F. & Bressan, R. A.Parkinson's disease and dopamine transporter neuroimaging - A critical review. Sao Paulo Med. J. 2006; 124, 168–75.

22. Seifert, K. D. & Wiener, J. I. The impact of DaTscan on the diagnosis and management of movement disorders: A retrospective study. Am. J. Neurodegener. Dis. 2013; 2, 29–34

23. Brigo, F., Matinella, A., Erro, R. & Tinazzi, M. [123I]FP-CIT SPECT (DaTSCAN) may be a useful tool to differentiate between Parkinson's disease and vascular or drug-induced parkinsonisms: A meta-analysis. Eur. J. Neurol. 2014; 21, 1369–e90

24. Bajaj, N., Hauser, R. A. & Grachev, I. D. Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. J. Neurol. Neurosurg. Psychiatry. 2013; 84, 1288–95 .

25. Spiegel, J. et al. Striatal FP-CIT uptake differs in the subtypes of early Parkinson's disease. J. Neural Transm. 2007; 114, 331–35.

26. Booij, J. et al. FP-CIT SPECT shows a pronounced decline of striatal dopamine transporter labelling in early and advanced Parkinson's disease. J. Neurol. Neurosurg. Psychiatry.1997; 62, 133–40

27. Benamer, H. T. S. et al. Correlation of Parkinson's disease severity and duration with 123I-FP-CIT SPECT striatal uptake. Mov. Disord.2000; 15, 692–98.

28. Booij J, Teune LK, Verberne HJ. The role of molecular imaging in the differential diagnosis of Parkinsonism. Q J Nucl Med Mol Imaging 2012; 56(1):17-26.

29. Antonini, A. et al. 123I-Ioflupane/SPECT binding to striatal dopamine transporter (DAT) uptake in patients with Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. Neurol. Sci. 2003;24, 149–50

30. Black KL, Hawkins RA, Kim KT, Becker DP, Lerner C, Marciano D. Use of thallium-201 SPECT to quantitate malignancy grade of gliomas. J Neurosurg. Sep 1989;71(3): 342-46

31. Léveillé J, Pison C, Karakand Y, Lemieux R, Vallières BJ. Technetium-99m glucoheptonate in brain-tumor detection: An important advance in radiotracer techniques. J Nucl Med 1977; 18:957-61.

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CASE REPORTS

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

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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 heterotopias 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*geneare 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.

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2. Dr. Kazi Gias Uddin Ahmed, Associate professor and Head, Dept. of Neurology, DMCH, Dhaka.
3. Dr. Mohammad Aftab Rassel, MD thesis student, Dept. of Neurology, DMCH, Dhaka.

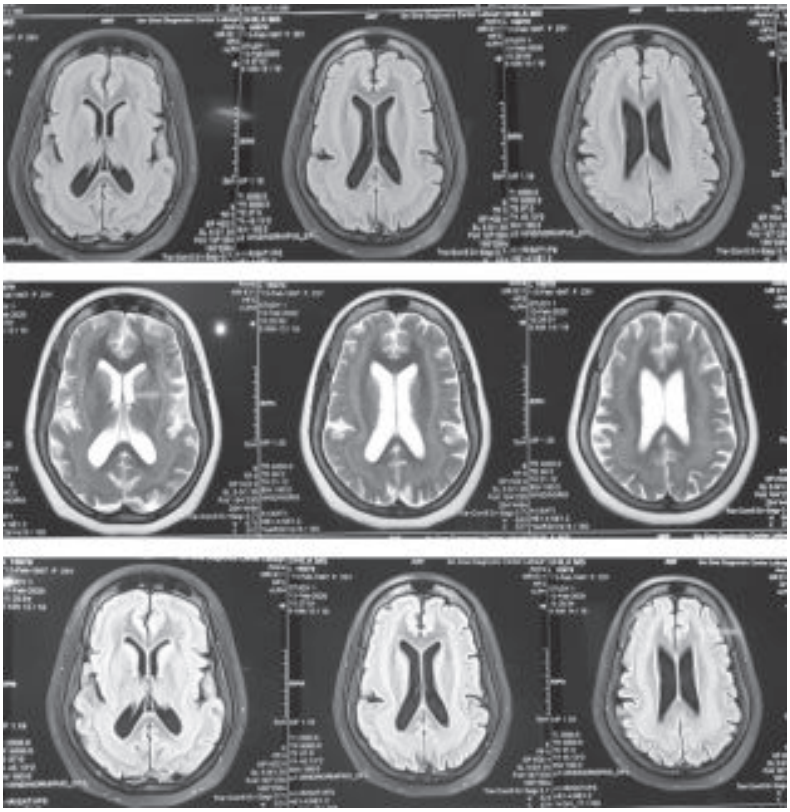

Fig.-1: *MRI of Brain T1 T2 FLAIR sequence revealed a band of grey matter located deep to, and roughly paralleling, the cortex, with pachygyric overlying cortex. The band of abnormal grey matter is complete. There is posterior predilection.*

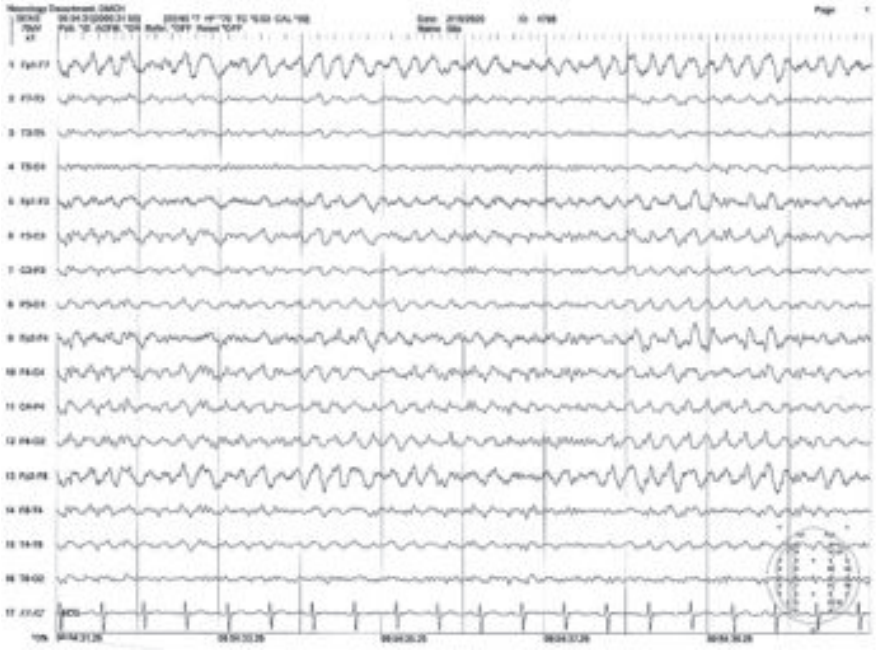

Fig.-2: *EEG in bipolar montage revealed Bi-Frontal intermittent rhythmic delta.*

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 in 19%-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 could 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

References:

1. Jacob H. Faktorenbei der Entstenhung der normalen und entwicklungsgestortenHirnrinde. Z Neurol Psychiatry (Orginalien) 1936;155:1-39
2. BarkovichAJ, Jackson DE Jr. Boyer RS. Band heterotopia: A newly recognized migration anomaly. Radiology 1989; 171:455-8.
3. Palmini A, Andermann F, AicardiJ.Diffuse cortical dysplasia, or the 'double cortex syndrome':the clinical and epileptic spectrum in 10 patients. Neurology 1991;41:1656-62
4. Dobyns WB, Guerrini R, Leventer RL. Malformations of cortical development. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors. Swaiman's Pediatric Neurology: Principles and Practice. ed 5. Edinburgh: Elsevier Saunders; 2012. pp. 202–231.
5. Bahi-Buisson N, Souville I, Fourniol FJ, Toussaint A, Moores CA, Houdusse A, Lemaitre JY, Poirier K, Khalaf-Nazzal R, Hully M, Leger PL, Elie C, Boddaert N, Beldjord C, Chelly J, Francis F; SBH-LIS European

Consortium. New insights into genotype-phenotype correlations for the doublecortin-related lissencephaly spectrum. Brain. 2013 Jan; 136(Pt 1):223-44. doi: 10.1093/brain/aws323.

6. González-Morón D, Vishnopolska S, Consalvo D, Medina N, Marti M, Córdoba M, Vazquez-Dusefante C, Claverie S, Rodríguez-Quiroga SA, Vega P, Silva W, Kochen S, Kauffman MA. Germline and somatic mutations in cortical malformations: Molecular defects in Argentinean patients with neuronal migration disorders. PLoS One. 2017 Sep 27; 12(9):e0185103. doi: 10.1371/journal.pone.0185103. eCollection 2017.
7. D'Agostino MD, Bernasconi A, Das S, et al. Subcortical band heterotopia (SBH) in males: clinical, imaging and genetic findings in comparison with females. Brain. 2002; 125:2507–22.)
8. Neuronal migration disorders, genetics, and epileptogenesis.Guerrini R, Filippi TJ Child Neurol. 2005 Apr; 20(4):287-99.
9. Barkovich AJ, Kjos BO. Gray matter heterotopias: MR char-acteristics and correlation with developmental and neuro-logic manifestations. Radiology 1992; 182: 493-99.
10. D'Agostino MD, Bernasconi A, Das S. et-al. Subcortical band heterotopia (SBH) in males: clinical, imaging and genetic findings in comparison with females. Brain. 2002;125 (Pt): 2507-22.

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Cerebellar Ataxia with Progressive Optic Atrophy and Deafness (CAPOS Syndrome): A Rare Case Report

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Abstract

CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, sensorineural hearing loss) is a rare autosomal dominant disorder caused by ATP1A3 mutation. Fever triggered cerebellar dysfunction along with progressive optic atrophy and sensorineural deafness are typical features. Herein, we report a 20-year-old female with multiple fever induced cerebellar dysfunction with partial improvement. Pendular nystagmus and optic atrophy were prominent which were also present in patient's younger sister. As there was progressive sensorineural hearing loss and areflexia, CAPOS syndrome was diagnosed. Though specific therapy is yet to be developed, acetazolamide, cochlear implantation, visual aid and family screening may improve quality of life.

Key words: *CAPOS syndrome, cerebellar ataxia, optic atrophy, hearing loss, ATP1A3 mutation.*

Introduction:

CAPOS syndrome, which is derived from the acronym of symptoms like cerebellar ataxia, areflexia, pes cavus, optic atrophy, sensory neural hearing loss, is a very rare disorder; first described in three patients by Nicolaides et al. in 1996[1]. Since the original description, about forty patients have been reported and causal association with specific genetic mutation has been established[2]. A missense mutation of the ATP1A3 gene, inherited as autosomal dominant traits with variable expressivity, causes the allelic disorders namely: CAPOS syndrome, rapid – onset dystonia-parkinsonism (RDP) in DYT12 and alternating hemiplegia of childhood (AHC)[3]. The typical CAPOS phenotype presents in infancy to early childhood with recurrent episodes of neurological dysfunction usually triggered by non-specific febrile illness[4]. Usually there is one to three paroxysmal episodes of cerebellar ataxia, areflexia, hypotonia, motor weakness, ophthalmoparesis, lethargy and/or comatose state that resolve within days to weeks, leaving residual ataxia, areflexia as the deafness and optic atrophy gradually deteriorate[5,6]. Less-well reported features include seizures, choreo-athetosis, dystonia, autistic features, mild learning disabilities which may suggest partial overlap of other ATP1A3-related disorders (RDP & AHC) with CAPOS phenotype[7]. But it is the progressive optic atrophy and sensorineural deafness along with cerebellar ataxia that differentiates CAPOS phenotype from others[7,8].

Here, we report the case of a CAPOS syndrome with typical presentation, who also has a sibling showing early features of the same syndrome.

Case Report:

The patient is a 20-year-old Bangladeshi female, who is the first issue of healthy consanguineous parents. She was born at term after an uneventful pregnancy by normal vaginal delivery. Her birth weight was more than 2500 gram with no features of perinatal asphyxia. Her growth and development were age appropriate up to 8 months of age, after which she developed non-specific fever for 2 days.

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During the febrile episode, she showed irritability, lethargy, hypotonia and pendular movement of both eyes. She also showed occasional sudden jerky movement of hands and feet, 2-3 times per day. She was hospitalized and treated with intra-venous medications and fluid and responded within days. As her condition improved, she showed persistent pendular movement of both eyes with difficulty in eye fixation. She had mild developmental delay showing clumsiness in standing and walking. But she could walk independently at 2.5 years.

At about 10 years of age, she developed fever for 3-4 days with decreased muscle power, diminished responsiveness and inability to walk. But within few days her condition improved as she could walk independently again. But her parents noticed, her speech became slurred with some word becoming more difficult to pronounce. Her eyes became shakier; she showed more difficulty on walking on uneven surfaces. She had difficulty fixating her eyes to text and also hearing faint sound became problematic for her. As a consequence her school performance became poorer. They consulted ophthalmologist who prescribed spectacles and advised reading in well illuminated conditions. But gradually her hearing and vision diminished. Initially she had corrected vision of 6/6 with spectacles. But within years her best corrected vision became 6/36 bilaterally. As for her hearing, audiometry initially showed mild sensorineural deafness that progressively became moderately severe bilaterally. She also developed occasional myoclonic jerking involving part of body for which she was evaluated by a neurologist who advised electro-encephalogram and prescribed anti-epileptic drug with which her jerking improved.

She stopped school at 16 years of age at class nine due to poor vision and hearing. Her age of menarche was at 13 years. Her menstrual cycle was regular with average flow. She was unmarried. She was immunized according to national immunization schedule. All her family members except for her younger sister were in good health. There was no history of such illness in her family members.

At time of presentation to us, she was alert with body built below average. Vitals were within normal limit with no anemia, jaundice, clubbing, thyromegaly, lymph node enlargement. She had no abnormal skin pigmentation, high arched palate, scoliosis, pes cavus or any chest deformity. Nervous system examination revealed, she was oriented in time, place and person, memory was normal, intelligence below average, and speech was slurred with inability to pronounce properly. She occasionally talked to herself, but there was no abnormal thought or any abnormal neologism. Regarding cranial nerve examination, her eye had full range of motion with pendular horizontal nystagmus that showed no fatigue or latency. Fundoscopy revealed bilateral primary optic atrophy and Rinne-Weber test revealed bilateral sensorineural hearing loss. All other cranial nerves were intact. Motor system revealed normal muscle bulk with hypotonia, power of all 4 limbs were MRC grade5. All jerks were diminished to absent with re-inforcement and planter were bilaterally flexor. She had no abnormal movement of any part of body at rest. Her co-ordination was impaired as evidenced by dysmetria, dysdiadochokinesia and abnormal heel-shin test. Her gait was broad based with irregular steps and her tandem gait was impaired. She had difficulty walking on uneven surfaces and going up/ downstairs. All modalities of sensation including vibration and position sense were intact. She could do her activities of daily life without any support.

She underwent extensive investigation and consulted different physicians of different specialties. List of her investigation profile is given below. But except for optic atrophy and sensori-neural hearing loss, all her investigations revealed no clue to the cause of her abnormality. The only investigation that could have been done to establish the etiology was genetic analysis, but patient party refused to proceed further for lack of financial support.

Patient's younger sister, 8 years of age also had pendular movement of both eyes along with impairment of tandem gait, triggered by febrile illness. She had no other cerebellar feature. She also had mild visual difficulties and optic disc pallor. Her hearing was normal at bedside testing. She had no pes cavus. The patient's younger brother was quite normal.

Laboratory investigations done on the patient

Blood	Complete blood count, ESR, CRP, glucose, urea, creatinine, electrolytes, liver function, thyroid hormone, iron profile, creatine kinase, Antinuclear and anti-pospholipid antibody, ANCA, VDRL, hepatitis B&C antibody, ceruloplasmin, vitamin B12, folate
Urine	Routine examination, culture sensitivity, copper
CSF	Cytology, protein, glucose, VDRL, ADA, lactate, Gram & AFB stain, Gene xpert for MTB, oligo-clonal band & Ig-G index
Imaging	Chest Xray, Ultrasonogram of whole abdomen, ECG, Echocardiogram, MRI of brain and orbit, slit lamp examination for KF ring
Neuro-physiology	Electro-encephalogram, nerve conduction study

Discussion:

Cerebellar ataxia may impose a diagnostic dilemma as there are many differentials, but the age of onset, speed of progression, family history and concomitant other features may provide clue to the final diagnosis[5]. CAPOS syndrome is a rare differential of cerebellar syndrome. Though first described in 1996, it remains a rare condition and the underlying pathogenesis is yet to be fully described[4].

This is the first case report of CAPOS syndrome from Bangladesh, to the best of our knowledge. Among the core features, our patient did not have pes cavus. All the case reports that have been published so far, only 30% of them had pes cavus[9]. As a matter of fact, some authors also suggested changing the acronym to "CAOS" syndrome; as all the patients did not have pes cavus[6]. Our patient presented with the typical history of more than one fever induced cerebellar ataxia with encephalopathic features and weakness with partial remission. But her nystagmus and areflexia persisted as the vision and hearing gradually deteriorated, which is consistent with typical presentation[7,10]. She also had delayed milestone of development, mild intellectual impairment and few episodes of seizure which are among less-well reported features; but are consistent with spectrum of ATP1A3 mutation phenotype[11]. The patient and her younger sister were affected among three siblings, which may indicate the autosomal dominant pattern of inheritance. But as the parents were not affected, it might be the de novo mutation that may explain the disease, which is also well reported[5].

CAPOS syndrome is caused by missense mutation of the ATP1A3 gene with replacement of 818th amino acid glutamic acid by lysine[5,6]. Other diseases RDP, AHC and most recently relapsing encephalopathy with cerebellar ataxia have also been attributed to the ATP1A3 mutation[12]. These disorders have overlapping features like early onset, triggered by febrile illness, polyphasic episodes with abnormal movements of different parts of body including eyes, seizure potentials and occasional intellectual disabilities[6]. But the differentiating features of CAPOS phenotype are the progressive bilateral optic atrophy and sensori-neural deafness[6].

During the acute episodes clinical features may be compatible with encephalitis or post viral cerebellitis; or if motor weakness is pronounced then atypical GBS[9]. Also due to the relapsing and remitting course, multiple sclerosis may also be considered. But the age of onset and absence of relevant imaging and CSF findings excluded MS. Again Friedreich's ataxia was also a differential but presence of hearing loss and absence of sensory neuropathy and abnormal imaging excluded this consideration.

ATP1A3 encodes for alpha 3 subunit of the Na^+/K^+-ATPase pump which is a ubiquitous transmembrane enzyme responsible for

maintaining cell membrane polarity[12]. The alpha 3 subunit is selectively present in the neurons of CNS, whereas alpha 2 subunit is expressed in the glial cells[10]. Alpha 3 subunit is also expressed in the afferent and efferent neurons innervating the skeletal muscle spindle which may explain the acquired areflexia without any electro-physiological evidence of peripheral neuropathy[6]. The sensori-neural hearing loss is attributed to auditory neuropathy and best treated with cochlear implantation as it directly stimulates the neural pathway[7]. Optic atrophy adds more obstacle in the way of communication as deaf persons often rely on visual cues for lip reading.

Till date, there is no established disease modifying therapy for CAPOS syndrome[7,9,10]. Carbonic anhydrase inhibitor acetazolamide has been reported to prevent relapse by generating a state of metabolic and brain acidosis, which may normalize neuronal excitability[5,9]. Supportive treatment with visual aid, cochlear implantation, speech therapy may improve quality of life to some extent[7].

Conclusion:

CAPOS syndrome is an autosomal dominant disorder presenting as cerebellar ataxia with progressive optic atrophy and sensori-neural deafness. When there is no imaging and electrophysiological evidence of any abnormality; CAPOS syndrome remains an important differential. Genetic analysis to see ATP1A3 mutation establishes the diagnosis. Supportive therapy along with acetazolamide may be of benefit. But counseling and screening of other family members are equally important.

Conflict of interests:

The authors declare that they have no conflict of interest.

References:

1. Nicolaides P, Appleton RE, Fryer A. Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS): a new syndrome. Journal of medical genetics. 1996 May 1;33(5):419-21.
2. Stenshorne I, Rasmussen M, Salvanos P, Tallaksen CM, Bindoff LA, Koht J. Fever-related ataxia: a case report of CAPOS syndrome. Cerebellum & ataxias. 2019 Dec 1;6(1):2.
3. Demos MK, van Karnebeek CD, Ross CJ, Adam S, Shen Y, Zhan SH, Shyr C, Horvath G, Suri M, Fryer A, Jones SJ. A novel recurrent mutation in ATP1A3 causes CAPOS syndrome. Orphanet journal of rare diseases. 2014 Dec 1;9(1):15.
4. Paquay S, Wiame E, Deggouj N, Boschi A, De Siati RD, Sznajer Y, Nassogne MC. Childhood hearing loss is a key feature of CAPOS syndrome: A case report. International Journal of Pediatric Otorhinolaryngology. 2018 Jan 1;104:191-4.
5. Maas RP, Schieving JH, Schouten M, Kamsteeg EJ, van de Warrenburg BP. The genetic homogeneity of CAPOS syndrome: four new patients with the c. 2452G> A (p. Glu818Lys) mutation in the ATP1A3 gene. Pediatric neurology. 2016 Jun 1;59:71-5.
6. Heimer G, Sadaka Y, Israelian L, Feiglin A, Ruggieri A, Marshall CR, Scherer SW, Ganelin-Cohen E, Marek-Yagel D, Tzadok M, Nissenkorn A. CAOS—Episodic cerebellar ataxia, areflexia, optic atrophy, and sensorineural hearing loss: A third allelic disorder of the ATP1A3 gene. Journal of Child Neurology. 2015 Nov;30(13):1749-56.
7. Tranebjærg L, Strenzke N, Lindholm S, Rendtorff ND, Poulsen H, Khandelia H, Kopec W, Lyngbye TJ, Hamel C, Delettre C, Bocquet B. The CAPOS mutation in ATP1A3 alters Na/K-ATPase function and results in auditory neuropathy which has implications for management. Human genetics. 2018 Feb 1;137(2):111-27.
8. Hayashida T, Saito Y, Ishii A, Hirose S, Hiraiwa R, Maegaki Y, Ohno K. Further characterization of CAPOS/CAOS syndrome with the Glu818Lys mutation in the ATP1A3 gene: a case report. Brain and Development. 2018 Aug 1;40(7):576-81.

9. Rodriguez AD, Prochazkova M, Santos SS, Cabezas OR, Extremera VC, Gonzalez-Gutierrez-Solana L. Early Diagnosis of CAPOS Syndrome Before Acute-Onset Ataxia—Review of the Literature and a New Family. Pediatric Neurology. 2017 Jun 1;71:60-4.

10. Carecchio M, Zorzi G, Ragona F, Zibordi F, Nardocci N. ATP1A3-related disorders: an update. European Journal of Paediatric Neurology. 2018 Mar 1;22(2):257-63.

11. Sweney MT, Newcomb TM, Swoboda KJ. The expanding spectrum of neurological phenotypes in children with ATP1A3 mutations, Alternating Hemiplegia of Childhood, Rapid-onset Dystonia-Parkinsonism, CAPOS and beyond. Pediatric neurology. 2015 Jan 1;52(1):56-64.

12. Dard R, Mignot C, Durr A, Lesca G, Sanlaville D, Roze E, Mochel F. Relapsing encephalopathy with cerebellar ataxia related to an ATP 1A3 mutation. Developmental Medicine & Child Neurology. 2015 Dec;57(12):1183-6.