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Relationship of Glycemic Status with Disease Severity in Guillain-Barré Syndrome

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Abstract

Background: Guillain-Barré syndrome (GBS) is an acute autoimmune polyneuroradiculopathy characterized by flaccid paralysis which may lead to respiratory failure requiring intensive care. **Objective:** The purpose of the present study was to explore the relationship between the fasting plasma glucose (FPG), hemoglobin A1c (HbA1c) and disease severity of GBS patients who are not known to have DM. **Methodology:** This cross-sectional study included adult GBS patients without having DM [age 35 (22-48) years, median (interqurtile range, IQR); 39 male 22 female] who were admitted to Neurology department, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh from July 2018 to June 2019. Demographics, clinical data were noted and FPG, HbA1c were measured. Disease severity were assessed by the GBS disability scale ranging from 0 to 6 with increasing score reflecting increased disability. **Results:** Patients with more severe GBS (disability score ≥4, unable to walk) had higher frequency of elevated FPG >5.5 mmol/L (61.2%; 30/49) in comparison to those with less severe GBS (disability score ≤3, able to walk; FPG >5.5 mmol/L in 16.7%, 2/12; p=0.006). But distribution of HbA1c category was not different across the groups (disability score ≥4 vs. ≤3: HbA1c <5.7: 40% vs. 58%; 5.7-6.4: 50% vs. 25%; >6.4: 10% vs. 17%; p=0.296). Participants with elevated FPG were elder [elevated vs. normal FPG: 40 (28-54) vs. 25 (19-43) years; median (IQR), p=0.012] and had higher CSF glucose (p=0.002) than those with normal FPG, but there was no difference in respct of gender, MRC sum score, requirement of assisted ventilation, CSF protein, GBS subtypes and duration of hospital stay (p=not significant for all). **Conclusions:** Patients with severe GBS have higher frequency of elevated FPG but not HbA1c. An acute change in glucose metabolism may occur in GBS which needs further study. *[Journal of National Institute of Neurosciences Bangladesh, July 2020;6(2): 96-100]*

Keywords: Guillain-Barré syndrome; glycemic status

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Introduction

Guillain-Barré syndrome (GBS) is an acute autoimmune disorder of the peripheral nerves and their roots[1]. It often has a devastating clinical course leading to progressive symmetrical flaccid paralysis and eventual respiratory failure requiring intensive care. Even with the best treatment available death may occur in the acute progressive stage due to ventilatory insufficiency, pulmonary complications or autonomic disturbances. As the clinical course and outcome are highly variable, early

prediction of the disease course may help the clinicians to provide optimal management[2]. Multiple factors have been observed to be important for predicting prognosis of GBS. These factors include high age (aged 40 years and over), preceding diarrhoea (or C jejuni infection in the past 4 weeks), and high disability or muscle strength at nadir[3,4]. However, no biochemical marker has been well established that may be related to disease severity in GBS.

Several studies have obsereved some form of association between glycemic status and GBS[5-8]. Few patients with GBS was observed to have hyperglycemia during the acute phase of disease[5]. It is well known that aberrant immune response is associated with pathogenesis of both GBS and immune-mediated diabetes. Auto-antibodies to gangliosides is found both in GBS and type 1 diabetes as gangliosides are expressed in both the neurons and the islet cells[8]. As a result, there might be some mechanisms that impair beta cell insulin secretion during the acute immune insult in GBS which are yet to be defined. It has also been appreciated that, different cytokines play important roles in the pathogenesis of GBS[9]. These cytokines are also attributable for an increase in insulin resistance related to hyperglycemia[10]. Both impairment of insulin secretion and increase in insulin resistance may result in hyperglycemia of the patient in acute stage of GBS and blood glucose may serve as a marker of disease severity in GBS. Recently a study conducted by Wang et al. in China observed an association between fasting plasma glucose (FPG) and severity of GBS[11]. They observed a positive correlation of GBS severity with FPG but not to hemoglobin A1c (HbA1c) which indicates an acute change in plasma glucose with the onset of GBS. Moreover, hyperglycemia may also exacerbate the clinical and electrophysiological features influencing the long term disability in GBS[12].

GBS has marked regional variation in clinical phenotype, disease severity, electrophyological subtype, mortality and morbidity[13]. Outcome in respect to both mortality and morbidity are observed to be poor in Bangladesh in comparison to other parts of the world. Considering the differences of GBS patients in Bangladesh to that of other parts of the world, the present study aimed to explore the relationship between the FPG, HbA1c and disease severity of GBS patients admitted in department of Neurology, National Institute of Neurosciences and Hospital, Dhaka.

Methodology

This study included 61 adult patients with GBS admitted to the Department of Neurology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh from July 2018 to June 2019. Those who had received corticosteroid treatments and known to have diabetes were excluded from the study. Demographics, clinical symptoms, neurological findings, laboratory findings and treatment were noted in a semi-structured questionnaire. Participants with fasting glucose less than that of impaired fasting glycemia (≤5.5 mmol/L) according to criterion of American Diabetes Association[14], were assigned to normal fasting glucose group. Elevated fasting glucose level was defines as >5.5 mmol/L. HbA1c was categorized as normal (≤5.6%), prediabetes level (5.7-6.4%) and diabetes level (≥6.5%)[14]. Disease severity and functional impairments of the patients were assessed by the GBS disability scale, which is a widely accepted scale of disability for GBS patients ranging from 0 to 6 with increasing score reflecting increased disability[15]. GBS disabisity score ≤3 was regarded as less severe disease (able to walk) and ≥4 as more severe disease (unable to walk). Weakness in extremities was assessed using the Medical Research Council (MRC) sum score of six bilateral muscles in arms and legs, ranging from 0 (quadriplegic) to 60 (normal strength)[16]. Antecedent infection was detected by history. FPG and HbA1c were measured preferably on the same day of severity assessment at around 7th day of symptom onset. FPG was measured from venous blood by CLIA method (ci 4100, Abbot, USA) and HbA1c by HPLC method (ADAMS TM A1c, USA). Lumbar puncture and nerve conduction study (NCS) was done at around 10th day after symptom onset. The study was performed with approval of Ethical Review Committee of the institution. Written informed consent was taken from the patients or their guardian. Authors did not modify the usual mode of treatment determined by the treating physicians. Data were analyzed using IBM SPSS. Statistics for Windows version 22.0 (IBM Corp, Armonk, NY, USA). Quantitative data was expressed as mean and standard deviation if normally distributed, while median value with interquartile range (IQR) was used if not normally distributed. Qualitative data was expressed as frequency and percentage. For continuous variables, comparison between groups was made by the Students T-test or Mann-Whitney U test. Categorical variables were analyzed by the $\chi 2$ test. Statistical significance was accepted at p=0.05.

Results

Median age of the participants was 35 years (IQR 22 to 48) and there were male predominance (39/61; 63.9%).

The median FPG was 5.6 mmol/L (IQR 5.1 to 6.0) and median HbA1c 5.7% (IQR 5.4 to 6.1) (Table 1).

Table 1: Characteristics of the Participants (n=61)

Parameters	Median and IQR	Frequency (Percent)
Age in years	35 (22-48)	-
Gender		
• Male	-	39 (63.9)
• Female	-	22 (36.1)
Duration of hospital stay	-	11 (7-23)
Presence of antecedent infection	-	19 (31.1)
Pattern of antecedent infection		
• Diarrhea	-	12 (19.7)
• RTI	-	6 (9.8)
• Both	-	1 (1.6)
FPG mmol/L	5.6 (5.1-6.0)	-
*HbA1c%	5.7 (5.4-6.1)	-
GBS disability score		
• ≤3	-	12 (19.7)
• ≥4	-	49 (80.3)
MRC sum score (mean±SD)	21.4±13.9	-
Cranial nerve involvement	-	23 (37.7)
Requirement of assisted ventilation	-	17 (27.9)
CSF protein (mg/dl)	142.3 (83.8-265.7)	-
CSF glucose (mmol/L)	3.8 (3.6-4.4)	-
NCS finding		
• Demyelinating	-	24 (39.3)
• Axonal	-	37 (60.7)

*HbA1c was not measured in 1 participant; Percentages are over column total; FPG: fasting plasma glucose; IQR: interquartile range; RTI: respiratory tract infection; CSF: Cerebrospinal fluid; NCS: Nerve conduction study

FPG was ≤5.5 mmol/L in 29(47.5%) while the rest 32(52.5%) had elevated FPG [5.6-6.9 mmol/L in 27 (44.3%) and more than 7.0 mmol/L in 5 (8.2%)]. Distribution of HbA1c category was different across the FPG groups (p<0.001; Table 2).

Table 2: Distribution of HbA1c Category In Different Fasting Plasma Glucose Groups

*HbA1c	FPG (mmol/L)		
	≤5.5 (n=29)	5.6-6.9 (n=27)	≥7.0 (n=4)
≤5.6%	17 (58.6%)	9 (33.3%)	0 (0%)
5.7-6.4%	11 (37.9%)	15 (55.6%)	1 (25.0%)
≥6.5%	1 (3.4%)	3 (11.1%)	3 (75.0%)

by $\chi 2$ test, p<0.001; *HbA1c was not measured in 1 participant with ≥7.0 mmol/L FPG group; Percentages are over column total FPG: fasting plasma glucose; HbA1c: Hemoglobin A1c

Table 3: Fasting plasma glucose and HbA1c in GBS patients with different severity according to GBS disability score

Parameters	GBS disability score		P Value
	≤3 (n=12)	≥ 4 (n=49)	
FPG mmol/L			
• ≤5.5	10 (83.3%)	19 (38.8%)	0.006
• >5.5	2 (16.7%)	30 (61.2%)	
**HbA1c			
• ≤5.6%	7 (58.3%)	19 (39.6%)	
• 5.7-6.4%	3 (25.0%)	24 (50.0%)	0.296
• ≥6.5%	2 (16.7%)	5 (10.4%)	

*by $\chi 2$ test; **HbA1c was not measured in 1 participant; Percentages are over column total FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c

Table 4: Comparison of Clinical Characteristics of Participants in normal FPG group and elevated FPG group

Parameters	Normal FPG group (n=29)	Elevated FPG group (n=32)	P value
Gender			
• Male	20 (69.0%)	19 (59.4%)	0.436
• Female	9 (31.0%)	13 (40.6%)	
Duration of hospital stay (median, IQR)	10 (7-14)	12 (7-30)	0.235
Presence of antecedent infection	11 (37.9%)	8 (25.0%)	0.276
Pattern of antecedent infection			
• Diarrhea	7 (24.1%)	5 (15.6%)	
• RTI	4 (13.8%)	2 (6.3%)	0.437
• Both	0 (0.0%)	1 (3.1%)	
MRC sum score at nadir (mean±SD)	23.6±15.5	19.5±12.2	0.255
Cranial nerve involvement	12 (41.4%)	11 (34.4%)	0.573
Requirement of assisted ventilation	6 (20.7%)	11 (34.4%)	0.234
CSF protein (mg/dl, median and IQR)	157.5 (94.3-263.9)	126.9 (66.7-326.2)	0.576
CSF glucose (mmol/L, median, IQR)	3.6 (3.5-3.8)	4.0 (3.6-4.6)	0.002
NCS finding			
• Demyelinating	11 (37.9%)	13 (40.6%)	0.830
• Axonal	18 (62.1%)	19 (59.4%)	

*Comparison of normal FPG and high FPG group by unpaired t-test, Mann-Whitney U test or $\chi 2$ test as applicable; Percentages are over column total if not otherwise specified; FPG: fasting plasma glucose; IQR: interquartile range; MRC: Medical Research Council; CSF: cerebrospinal fluid

Patients with more severe GBS (disability score ≥4, unable to walk) had higher frequency of elevated FPG (61.2%; 30/49) in comparison to those with less severe GBS (disability score ≤3, able to walk; elevated FPG in 16.7%, 2/12; p=0.006; Table 3).

The distribution of HbA1c category was not different across the groups (disability score ≥4 vs. ≤3: HbA1c <5.7: 40% vs. 58%; 5.7-6.4: 50% vs. 25%; >6.4: 10% vs. 17%; p=0.296). Participants with elevated FPG were elder [elevated vs. normal FPG: 40 (28-54) vs. 25 (19-43) years; median (IQR), p=0.012] and had higher CSF glucose (p=0.002) than those with normal FPG, but there was no difference in respect of gender, MRC sum score, requirement of assisted ventilation, CSF protein, GBS subtypes and duration of hospital stay (p=not significant for all) (Table 4).

Discussion

The study evaluated the glycemic status in patients with GBS by measuring FPG and HbA1c and observed their relationship with GBS severety measured by disability scale score. A remarkable number of GBS patients had elevated FPG and HbA1c. Frequency of elevated FPG was significantly higher in more severe GBS group, which was not true for HbA1c. Elevated FPG group had higher age and higher CSF glucose but other parameters were not different when compared with those of normal FPG group.

GBS in Bangladesh has its own characteristics in comparison to other parts of the world[13,17]. Present study sample also represents these characteristics where median age of the participants was 35 years, predominant antecedent event gastroenteritis, median MRC sum score 21, diasability scale score ≥4 in 80% and nearly 30% requiring mechanical ventilation. Axonal subtype was remarkably higher among the participants, which is also a peculiarity of GBS in this particular region.

Glycemic status was assessed by FPG and HbA1c in the present study due to convenience of sampling. Nevertheless, a formal 75-g oral glucose tolerance test (OGTT) could better delineate the glycemic status of the patients. However, a large number of participants were observed to had FPG and HbA1c beyond the normal level (52.5% and 56.7% respectively), which was much higher than that previously reported in general population of Bangladesh[18]. In one third of the participants with elevated FPG, there was no elevation of HbA1c, reflecting an acute change of glycemic status. The acute change of plasma glucose in GBS has aloso been reported by several authors as case reports where GBS patients had coexistent acute complications of DM, eg. diabetic ketoacidosis[6,7]. Same immunological trigger may be responsible for such coexistence but it is yet to be proven[19].

The present study also observed that elevated FPG but not HbA1c was more common in GBS patients with disability score ≥4 in comparison to those with less severe GBS. This reflects a relationship between severity of GBS and plasma glucose of a patient. Similar relationship was also observed previously[11]. Some authors observed that DM is related to GBS outcome and influences long-term disability[12,20]. It is difficult to say whether DM increases GBS severity or severe GBS increases plasma glucose. A rise of inflammatory cytokines in both the conditions may be reposnsible for such association[9,10].

Blood glucose is not generally regarded as a marker of severity in GBS, rather age at onset, preceeding diarhhoea and MRC sum score at hospital admission are well known as poor prognostic factors[4]. In this study, it was observed that the age of the participants with elevated FPG was higher than those with normal FPG. Their might be some relationship between elevated FPG and age, but it is uncertain which one is directly related to the GBS severity and poor outcome. Elevated FPG group also had higher CSF glucose which reflects the physiological relation of blood to CSF glucose and may not be related to any pathophysiological mechanism.

The present study had several limitations. It was carried out in a single centre in Dhaka and so may not reflect the whole country. However, this is the only referral neuroscience institute of Bangladesh and hence patients are referred from all over the country. As a result the sample virtually represents the whole country. The authors could not assess changes of blood glucose over time in the entire course of GBS. In addition, the autoantibodies or cytokines levels which may be associated with blood glucose changes were also not assessed. Further studies in prospective manner are required to evaluate the matter.

Conclusion

In conclusion, glycemic abnormality is observed to be present in remarkable proportion of GBS patients. Severe GBS patients have higher frequency of elevated FPG but not HbA1c. An acute change in glucose metabolism may occur in GBS which needs further study.

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