Study of Autonomic dysfunction in patients with Guillain-Barré Syndrome (GBS)

Dissertation submitted to the The Tamilnadu Dr.M.G.R.Medical University, Chennai,Tamil Nadu, in fulfillment of the DM –Neurology University examinations in August 2011

CERTIFICATE

This is to certify that the Dissertation titled "Study of autonomic dysfunction in patients with Guillain-Barré Syndrome (GBS)" is the bonafide work of Dr .Zeyaur Rahman Azad submitted in fulfillment of the DM - Neurology examination conducted by the Tamil Nadu Dr. M.G.R Medical University, Chennai, in August 2011

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LIST OF ABBREVIATIONS

AIDP	Acute inflammatory demyelinating Polyradiculoneuropathy
AMAN	Acute motor axonal neuropathy
AMSAN	Acute motor sensory axonal neuropathy
ANS	Autonomic nervous system
ATs	Autonomic function test
BP -	Blood Pressure
bpm	Beat per minutes
CSF	Cerebrospinal fluids
CV R-R	Coefficient of variation of R-R intervals
DS	Disability score
EMG	Electromyography
EAN	Experimental autoimmune neuritis
GBS	Guillain Barre Syndrome
HR	Heart Rate Response
IV Ig	IV Immunoglobulin
NTAS	Normalized Total Autonomic Score
OH -	Orthostatic Hypotension
PNS	Peripheral nervous system
PTI -	Postural Tachycardia Index
PE	Plasma exchange
PCBP	Postural change of Blood pressure
PRES	Posterior reversible encephalopathy syndrome
P- Value	Probability value
RRIV	RR interval variability
SSR	Sympathetic skin response
SSwR	sympathetic sweat response
SBP	Systolic blood pressure
STD	Standard Deviation
VR	Valsalva ratio

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ABSTRACT

TITLE- -Study of autonomic dysfunction in patients with Guillain-Barré syndrome (GBS)

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INTRODUCTION- Guillain Barre syndrome is an immune mediated inflammatory disease of the PNS characterized by rapidly evolving symmetrical limb weakness, loss of tendon reflexes and absent or mild sensory signs .Autonomic neuropathy is an important and common complication of Guillain-Barré syndrome (GBS) and may be life threatening at time.The available studies showed variable incidence of autonomic dysfunction in GBS and its relation with the severity of motor paralysis and sensory disturbances.

OBJECTIVES- To study autonomic nervous system involvement in a group of patients' with Guillain- Barré syndrome (GBS) to assess its clinical significance and relation with clinical severity of GBS and its subtypes.

METHODOLOGY: Continuous recording of HR and BP and longitudinally performed autonomic function tests', including HR response to deep breathing and standing,valsalva ratio,postural change of systolic BP and cold immersion test were done once daily for the first 3 days of admission followed by once every week . The recordings' were continued till the 4th week of illness or improvement by 1 functional grade (Hughe's Grading), whichever was earlier.

RESULTS: 8 patients (7AIDP/IAMAN) were included for longitudinally performed autonomic function tests' (ATs). Autonomic dysfunction were detected in 7/8 patients

(87.5%) including one AMAN. Two patients (25%) had dysautonomia of severe grade with NTAS >16. Symptoms of dysautonomia were reported in 6/8 patients (75%) of which it was started 1-5 days before the onset of motor weakness in 3 patients. The most frequent manifestation of dysautonomia in our patients was sinus tachycardia (87.5%) followed by Hypertension,labile HR and labile BP(75 % each).Episodes of hypotension was reported in 50% patients where as bradycardia in 37.5% patients. HR response to deep breathing (I-E differences) was abnormal in 3/ 6 patients (50%), where as HR response to active standing (30:15 ratio) 1/2 patients who was able to perform the test . Valsalva ratio was abnormal in one of 2 patients (50%). 62.5% of patient fails to rise of diastolic BP significantly in Cold immersion test where as 50 % patients who was able to stand unsupported was showing significant fall of systolic BP on standing at or before 3 min. SSR was absent in 62.5% patients (4 AIDP /1AMAN) in both upper and lower limbs. All patients in whom SSR was absent , had evidence of dysautonomia.

CONCLUSION:The present study demonstrated high incidence of autonomic dysfunction in patient with GBS (87.5%). Fifty percent patients had evidence of both sympathetic and parasympathetic dysfunction ,25 % patients predominantly sympathetic dysfunction where as 12.5% patients had predominantly parasympathetic dysfunction.The presence and severity of dysautonomia(NTAS) was not related to motor disability ,sensory disturbances and use of mechanical ventilation but was correlated with older age (>45 yrs) of onset of illness.

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INTRODUCTION

Guillain Barre Syndrome is an immune mediated inflammatory disease of the peripheral nervous system characterized by rapidly evolving symmetrical limb weakness, loss of tendon reflexes, absent or mild sensory signs and variable degree of autonomic dysfunction and cranial nerve involvement. The clinical spectrum consists of four major subgroups - Acute inflammatory demyelinating polyradiculo neuropathy (AIDP), Acute motor axonal neuropathy (AMAN), Acute motor sensory axonal neuropathy (AMSAN) and Miller–Fisher syndrome.Autonomic neuropathy is an important and common complication of Guillain-Barré syndrome (GBS) and occurred in approximately two-third of patients [1,2].Most of the previous studies of autonomic dysfunction in GBS are those with AIDP, except a study from China comparing autonomic dysfunction between AMAN and AIDP[3] and from Taiwan, who studied cardiovascular autonomic dysfunction in nine of Miller Fisher syndrome[4].These small studies had shown different patterns and severity of dysautonomia in GBS and its variants', probably due to difference in immunopathogenesis and target molecules. A wide range of symptoms have been described including arrhythmias of various type, abnormal fluctuation of blood pressure and heart rate, gastrointestinal and genitourinary dysfunction ,sweating abnormalities ,abnormal hemodynamic response to drug and tracheal suction.Signs of Sympathathetic and Para sympathetic failure may be present as well as over activity of sympathetic and parasympathetic nervous system. Both features may be present even in the same patient. The lesion may occur in the afferent arterial baroreceptors,sympathetic efferent's to arterioles and veins or in the efferent cardiac parasympathetic innervations carried in the vague nerve[5].Some patients with Guillain-Barré syndrome have severe autonomic dysfunction that can be life threatening and may require the placement of a cardiac pacemaker. Serious arrhythmias was thought to occur in severely disabled patient, mainly

in those who needed mechanical ventilation[6] ,recent study indicate that these life threatening complication may also developed in less severely affected patient even in those who were still able to walk more than 5 meters. Majority of the available studies showed no correlation between degree of dysautonomia and severity of motor paralysis, sensory symptoms and motor nerve conduction velocities[7]Available studies indicated that dysautonomia recovered with recovery of motor paralysis.Most of the available studies on autonomic dysfunction in GBS were done on limited number of patients, mainly AIDP.Inspite of emergence of PE and IVIg as a treatment option in GBS during last three decades', that halts the progression of disease and shortens' the duration of illness but fatality of GBS remains unchanged [8,9] which is mainly due to dysautonomia.Since dysautonomia is an important factor responsible for fatalities in this disease,patients with dysautonomia should be monitored closely until they recovered from it. The pattern and prognosis of autonomic dysfunction in GBS require more number of studies on larger number of patients including axonal variants of GBS, which would help to understand this much better and utilize this in clinical practice, to pre-empt, detect and treat life threatening dysautonomia and thereby avoid fatality.

Epidemiology of GBS: GBS is the most common cause of post infectious neuromuscular weakness world wide .The incidence rate varies between 0.6-4 cases per 100,000 population [10,11] the lifetime likely hood for an individual developing GBS is approximately 1:1000 [12] The GBS can occur at any age with attack rate's being higher in persons' between 50-74 yrs of age [13] but in china the incidence rate is about the same in child hood and much less in adult than in adult elsewhere. Most cases are sporadic ,but small cluster have been associated with outbreak of bacterial enteritis caused by contaminated water [14] and summer epidemics in northern china ,probably due to infection with Campylobacter jejuni [15]

Antecedent Events in GBS:

About 2/3rd of GBS patients report a preceding event 1-4 weeks prior to onset of neurological symptoms. Prior infection is well established as a precipitating event in the development of GBS. Most antecedent illnesses associated with GBS affect the upper respiratory tract, followed by GI tracts.

Antecedent Events	Percentage
Respiratory illness	58%
Gastrointestinal illness	22%
Respiratory illness and Gastrointestinal illness	10%
Surgery	5%
Vaccination	3%
Others	2%

[16](Govoni and Granieri -2001)

The specific infectious agent related to GBS includes:C.Jejuni,Mycoplasma Pneumoniae,CMV,Varicella Zoster,EBV ,HIV,Hepatitis A and Hepatitis B.

The preceding infection detected serologically in 2 large series with GBS are

	Netherland (n=476) 1987-96	North America and Europe(n=383) 1993-1995
C.Jejuni	32	23
Cytomegalo Virus	18	8
Epstein Barr Virus	7	2
Mycoplasma Pneumoniae	9	Not tested

Campylobacter jejune is the most common identifiable organism linked to GBS particularly , the axonal form.The evidence of C.jejuni infection from Stool culture and serological tests' in patient' admitted with GBS varies in different parts of the world,

specially having in northern China where infection rate of 76% was seen in patients with AMAN and 42% in patient with AIDP were found [17] The C. jejune is a gram negative rod is common cause of bacterial enteritis world wide .It is characterized by watery /bloody diarrhoea and abdominal cramping.

Study have shown that the lipopolysaccharides of these organisms share ganglioside like epitopes with peripheral nerves .[18] This molecular mimicry appears to confuse the immune system, resulting in mistaken attack against neural antigens. The development of GBS only in certain percentage of C.Jejuni infected patient is probably related to host factor or certain Polymorphism of C.jejuni.[19]

.Clinical features of GBS:Typical GBS is an acute, predominantly motor neuropathy presenting as distal limb paresthesias, relatively symmetric limbs weakness, and frequent gait ataxia. Fever or other constitutional symptoms are absent at the onset of illness.The usual pattern is an ascending paralysis evolving over hours to few days. Proximal muscle weakness occurs very frequently, especially initially, with subsequent distal arm and leg weakness. In about 15% cases of GBS, a descending pattern of weakness is seen [20] .Usually, symmetric distal limb paresthesias develops (in about 50 % cases of GBS) before clinically evident limb weakness.Sensory loss is not an important features of GBS and frequently limited to distal impairment of vibration sense. Pain of moderate to severe grade occur in about 2/3rd of GBS patient mainly at the onset of illness.[21]Reduced or absent deep tendon reflexes are seen at the onset or within first few days of onset of symptoms.The early loss of reflexes may be due to desynchronization of afferent impulses in reflex arc due to non-uniform demyelination.Involvement of Cranial nerves' are seen 45%-75% cases of GBS in different series. [22] Facial paresis usually bilateral is found in at least 50% cases of GBS.The proportion of patients developing respiratory failure following diaphragmatic or Respiratory muscles involvement and requiring assisted ventilation varies between 13%-30 % in different

Series .[23]Dysautonomia is common and may occur even in milder form of GBS. Usual features are loss of vasomotor control with wide fluctuation in blood pressure, postural hypotension, and cardiac dysrrhythmias and can be life threatening and required close monitoring and management. [24]There may be postural dizziness,palpitation, increased thirst,bladder and bowel dysfunction and sweating abnormalities.

Variants of GBS: Depending upon topography,Clinical course ,types of fiber involved and Pathological features patient of GBS can be classified into following sub type

1) Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)

2) Acute Motor Axonal Neuropathy (AMAN)

3) Acute Motor and Sensory Axonal Neuropathy (AMSAN)

4) Miller-Fisher syndrome

5) Pan dysautonomia

6) sensory GBS

7) Polyneuritis cranialis

Course and prognosis of GBS:The disease reaches its nadir by 2 weeks in most cases and in 4 weeks in nearly all patients'. After progression stops, patients' enter a plateau phase lasting for 2-4 weeks, and recovery begins with return of proximal followed by distal strength over weeks or months [25]. According to studies,72 % of patient have complete recovery in 1 year and 82% in 2 years time. [26]The most common residual difficulties are weakness of the lower leg muscles, numbness of the feet and toes, and mild bifacial weakness. A few patients are left with a sensory ataxia, which may be disabling Distal neuropathic pain and persistent autonomic problems occur but are infrequent. The mortality rate varies between 2-7% of patient in different series.[27,28.]In the early stages, death is most often due to cardiac arrest. perhaps related to dysautonomia and later in the illness,

pulmonary embolism and infectious complications of prolonged immobilization and respiratory failure are the main causes.In several studies ,preceding diarrhoeal illness, C.jejuni infection had more severe disease and a delayed recovery when compared with other patients'[29]

Pathogenesis of GBS: The clinical and experimental evidence suggest that GBS is an organ specific immune mediated disorder caused by interaction of cell mediated and humoral immune response to peripheral nerve antigen [30,31].A preceding infection may trigger an auto immune response through molecular mimicry.The infectious agents have epitopes on their surface that are similar to epitopes on the surface of peripheral nerves (e.g., gangliosides, glycolipids,resulting in the peripheral nerve acting as a ''molecular mimic'' of the infectious agent. [32] As carbohydrate moieties of gangliosides (e.g., GM1, GD1a, GQ1b) found on the surface of the peripheral nerve are structural mimics of the lipo oligosaccharides (LOSs) of C. jejune.[33] Initially activated T cells play a major role in the opening of blood nerve barrier and allow circulating antibody to gain access to peripheral nerve antigen.The activation marker of T cells (IL-6,IL-2,Soluble IL-2 receptor and INF Y) and pro inflammatory cytokines released by T cells and macrophages ,TNF alpha are increased in patient serum.Soluble E selecting, adhesion molecules and matrix metalloproteinase's are increased in early stage of patients with GBS and are involved in facilitating recruitment and transmigration of activated T cells and monocytes through the blood nerve barrier.A cell mediated immune response against the myelin component is supported by Experimental autoimmune Neuritis, the accepted animal model for AIDP.

Experimental autoimmune neuritis:The pathology of AIDP closely resembles that of experimental autoimmune neuritis induced in animal by active immunization with whole peripheral nerve homogenate, myelin or PNS specific myelin basic protein P2,P0,P22 or galactocerebroside. [34] Study indicate that humoral factors also having significant role in the pathogenesis of GBS and participate in the autoimmune attack on peripheral nerve myelin,axon and nerve terminals as [35]

a) Immunostaining shows deposition of immunoglobulin and complement on the myelinated fiber of affected patient.

b) AMAN and MFS are associated with specific type of anti ganglioside antibody

c)AMAN and MFS patient's sera contain Gig antibodies that block neuromuscular transmission in a mouse nerve-muscle preparation.

d)Injection of GBS serum intraneurally into rat sciatic nerve results in secondary T-cells infiltration of injection site at the time of hind limb weakness.

e) Complement C1-fixing anti peripheral nerve myelin antibody can be detected in the sera of patient in acute stage of GBS.

f)Clinical recovery after plasma exchanges or IVIg has suggested that humoral factors play a prominent role.

Pathogenesis of AIDP:The immune attack in AIDP appears to begins with binding of auto antibodies to specific epitopes on cell schwann membrane with with consequent activation of complement.The nature of epitope in AIDP is likely to be a glycolipid.The complement activation product with membrane attack complex are seen on the outermost schwann cell surface within days of onset of symptoms ,leads to vascular myelin changes followed by recruitment of macrophages and progressive demyelination.In severe cases secondary axonal degeneration occur probably secondary or by-stander consequence of

enzymes or radicals released by immune mediated inflammatory response directed against the myelin.

AMAN:Acute motor axonal neuropathy is caused by an antibody and complement mediated attack on axolemmal epitopes of motor fibres.The target epitopes are GM1 and asialo GM1-like gangliosides,which are present in the nodal intermodal membrane of motor fibers.[36] In AMAN, following deposition of activated complement component and immune globulins at the nodal axolemma, leads to disruption of par anodal space and entry of complement and immunoglobulin's along the axolemma with subsequent recruitment of macrophages to affected nodes. These macrophages are shown to invade the peril axonal space ,leading to axonal degeneration.[37] AMAN, antibody binding may alter sodium channel function leading to conduction block. The reversal of Gig -mediated conduction block before development of axonal degeneration may explain the relatively rapid improvement of many of acute axonal neuropathy cases.

AMSAN:The pathology of AMSAN resembles AMAN but in AMSAN both ventral and dorsal root are affected.There is similar pattern of paucity of lymphocytic inflammation consistent with antibody mediated pathogenesis.

Miller Fisher Syndrome:Pathophysiological features of Miller Fisher Syndrome shares many aspects with AIDP and Acute motor axonal neuropathy.Molecular mimicry between infection (e.g., C. jejuni)and surface components of peripheral nerve plays a key role leading to humoral and complement activation with MAC formation and nerve axon terminal damage.[38] The main difference between MFS and AIDP or Acute motor axonal neuropathy is the activation of anti-GQ1b and anti-GT1a antibodies in MFS that target occulomotor and bulbar nerves, which are nerves thought to have relatively high GQ1b and GT1a ganglioside densities.[39] The pre synaptic nerve terminal axons and peril synaptic Schwann cells are damaged in MFS.

Antibodies associated with GBS and its variants [40]

1) AIDP	unknown
2) AMAN	GM1,GM1b, GalNac-GD1a
3) AMSAN	GM1,GM1b,GD1a
4) Miller-Fisher syndrome	GQ1b,GT1a
5) Pan Dysautonomia	
6) Sensory GBS	GD1b
7) Polyneuritis cranialis	GT1a

AIMS AND OBJECTIVES OF STUDY .

1) To study autonomic nervous system involvement in a group of patient of Guillain- Barré syndrome (GBS)
2) To assess the clinical significance of the autonomic nervous system involvement in such patients.
3) To assess the relation of autonomic dysfunction with clinical severity of GBS

REVIEW OF LITERATURE

Autonomic neuropathy is an important and common complication of Guillain-Barre syndrome (GBS).The neuropathy may involve visceral afferent fibers sub serving the autonomic nervous system (ANS), parasympathetic efferent fibers, sympathetic efferent's, or a combination of these territories. Manifestations may be present in Cardiovascular, Genitourinary, Gastrointestinal,Sudomotor and other systems involving both sympathetic and parasympathetic fibers to a different degree. There are a few studies' in literature, with variable examination of the autonomic nervous system. The literature suggests that the incidence of autonomic disease in GBS varies directly with the intensity of the search.[41] .

Experimental models of autonomic neuropathy in GBS

The most accepted model of GBS is experimental allergic neuritis (EAN),having evidence of involvement of autonomic nervous system mainly of myelinated structures of both sympathetic and parasympathetic arms.Waksman and Adams, who originally described EAN in rabbits reported lesions at the origin of the sympathetic white ramie communicans with preservation of sympathetic ganglia [42]. Tuck et al later provided evidence that autonomic myelinated fibers were targets of EAN in the guinea pig [43]. Tuck observed fall in amplitude of the vague and splanchnic nerve compound action potential, temporal dispersion and a reduction in conduction velocity and on histological evaluation demonstrated evidence of demyelination in 25% of the vague nerves studied and 56% of the splanchnic nerves. In addition there was reduction of density of myelinated fibers in both nerves and 30% of teased myelinated fibers were undergoing axonal degeneration. In the splanchnic, but not vague nerve, axonal degeneration and loss of unmyelinated fibers was observed in Tuck study. Thus, it appeared, in addition to the demyelinating changes, an apparent "broadening" of the pathologic insult to include axons of myelinated fibers and

unmyelinated fibers. Kalimo et al and Morey et al provided further morphologic data on rabbit EAN and rat EAN, respectively. In the rabbit study done by Kalimo et al there were changes in both sympathetic and parasympathetic structures with relative sparing of perikarya, and greater predilection for myelinated structures .[44]In the rat study of Morey et al autonomic involvement was largely limited to myelinated structures in the vague, but not sympathetic chain.[45.] Two physiologic studies of autonomic function in EAN done by Solders et al and Saksa et al almost at the same time and provide evidence that vagal neuropathy is an important feature In GBS. Solders et al. induced EAN in rats and observed, in some animals, a reduction in RR variability, mild vagal inflammation and demyelination and slowed conduction [46] where as Saksa induced EAN in rabbits and observed a loss in the bradycardic response to respiratory strain, suggesting vagal neuropathy [47].Appenzeller et al described a distinct experimental autonomic neuropathy in rabbits using human sympathetic ganglia tissue.The injected animals lost reflex vasodilation to trunk heating implying involvement of efferent sympathetic cholinergic fibers. Inflammatory changes were also observed in the sympathetic ganglia in this model.[48]

Pathological models of autonomic neuropathy in GBS

There have been only a few detailed pathologic studies of the autonomic nervous system involvement in GBS available till now. The studies available tend to support the physiological evidence that there are independent derangements of sympathetic and parasympathetic output as well as their afferent input. Haymaker and Kernighan reported edema and inflammation in the superior cervical sympathetic ganglion in one autopsy case.[49]In Matsuyama and Haymaker study ,vague nerve was showing occasional disintegrating ganglion cells, perivascular mononuclear cells, and demyelination where as the sympathetic nervous system had similar, but more mild changes. Axons and unmyelinated fibers were relatively well preserved,white ramie were often involved but grey ramie

rarely.[50]Later Birchfield and Shaw' described chromatoloytic changes in the inter mediolateral cell column of two autopsied patients, one of whom had postural hypotension prior to death where as one had abnormal Valsalva ratio.[51] Kanda et al described a patient with GBS who died of sudden bradycardia in which there were "myelin-destructive" lesions in the sympathetic chains and slight lymphocytic infiltrations in intracardiac ganglia. [52] Bredin et al mention infiltration with inflammatory cells of the stellate ganglion in one case with prominent autonomic instability .[53]Panegyres et al described a 41-year-old man that died on the twelfth day after onset of GBS from hypotension and asystole in which Sympathetic ganglia had chromatolysis, infiltrates of mononuclear cells, and nodules of nageotte, but there were also perivascular infiltrates in the hypothalamus and brain stem.[54]

The Nature of the Autonomic Deficit:

Reports of autonomic evaluation in patients with GBS has varied from single case studies to prospective investigations, often of selected patients using varying techniques and autonomic function test .

Cardiovascular complication:

Cardiovascular abnormalities in the GBS are attributed to autonomic neuropathy and are seen variably upto 2/3 rd of affected patients.[55]

Common benign complications :

1)Sinus tachycardia

2)Postural hypotension

3)Minor ECG changes

Serious Complications :

1) Hypertension (sustained, episodic)

2) Episodic hypotension

3) Sensitivity to vasoactive drug

4) Bradyarrhythmias (bradycardia, asystole)

5)Tachyarrhythmias

Alterations in resting blood pressure measurements and reflex blood pressure changes have implied that there is sympathetic dysfunction in GBS. Continuous blood pressure recordings have identified unpredictable fluctuation of blood pressure with sudden episodes of cardiovascular collapse. Fluctuations in BP are common and are thought to be characteristic of the GBS, helping to differentiate it from critical illness neuropathy [56] .Truax reported hypertension in 27% of GBS patients, paroxysmal in 24%, and sustained in 3%. Paroxysmal hypertension in Truax patient was correlated with quadriplegia and ventilatory dependence. [57]Sustained Hypertension may be complicated by subarachnoid hemorrhage, pulmonary edema or PRES.[58] Hypertensive episodes may be followed by abrupt hypotension or sudden death with extreme sensitivity to vasoactive agents. In McQuillan and Bullock study, systolic pressure fluctuations for over 3 min exceeded 50 mmHg,despite sedation and antihypertensive in one patient. In Lichtenfeld series,> 60% of patients' had either hypertension or electrocardiographic abnormalities , 43% had postural hypotension and episodic hypotension was seen in 57%.1 patient of Lichtenfeld series of patient had daily variation between 80/50 to 230/80 mmHg. Blood pressure elevations in Lichtenfeld's patients lasted for between 2 and 21 days from the onset of the illness with a mean of 7 days but, unlike Truax studies, there was no correlation between hypertension and severity of motor weakness [59].In the study by Pfeiffer et al, significant BP decreases were seen in about 75% of the patients' , although none reported any orthostatic symptoms, while patients with BP fluctuations and high diurnal heart rates have been identified as at high risk for arrhythmias as well [60,61].So, patients' with labile BP should undergo prolonged cardiovascular monitoring, preferably in an intensive care unit. In patients with hypotension,

a fluid challenge is advocated before starting low-dose vasopressin therapy. Presently, there are no specific recommendations for target mean arterial pressure. For sustained hypertension, the judicious use of anti hypertensive therapy is warranted. Patients with mean arterial pressure >125 mm Hg may be treated with intravenous labetalol, small, or nitroprusside. Ventilated patients on sedation should also be closely monitored for sudden fall in BP as well, especially given that the possibility of enervation hypersensitivity is high[62] In patient with labile BP, other contributing conditions, such as pulmonary thrombi embolism, sepsis, GI bleed,and metabolic abnormalities also need to be considered.

Parasympathetic dysfunction:

Most of the available studies suggest significant parasympathetic system defects in GBS. Vagal neuropathy probably has received the greatest attention. Vagal overactivity caused by afferent baron receptors reflex failure is believed to be responsible in causing bradycardia. Bradyarrhythmias can occur in up to 50% of patients with the GBS, and potentially serious events requiring the use of atropine or pacemaker placement, including atrio ventricular block and asystole, have been reported in 7% to 34% of patients [63,64,65]these vagal spells may be noted following tracheal suctioning [66] .Acute vagal deficit could be responsible for tachyarrhythmia, specially sinus tachycardia . In a study by Pfeiffer et al, an increase in the mean heart rate to >125 beats/min was documented in about 25% of the subjects. In the MGH series, sustained sinus tachycardia was noted in 37% of patients and that was correlating with the degree of motor weakness, the presence of respiratory failure and bulbar involvement. Persson and Solders had earlier noticed a reduction in rate-related R-R variation with normal and deep breathing in GBS patients.[67]Singh et al.reported abnormal expiratory/inspiratory heart rate ratio in 31.6% and an abnormal Valsalva heart rate ratio in 28.6% of their 24 patients with GBS [68]. Bansal et al. noted reduced mean heart rate acceleration to atropine in patients with GBS with later recovery implying a

parasympathetic afferent defect.[69] Other arrhythmias and ECG changes have been frequently reported In GBS patient including atrial tachyarrhythmias including fibrillation, Flutter, paroxysmal tachycardia, ventricular tachycardia, elevated or depressed ST segments, flat or inverted T waves, Q-T interval prolongation,axis deviation, and various forms of conduction block[70].These Electrocardiographic changes are believed to be secondary to associated myocardial involvement.

Myocardial involvement:

The myocardial involvement could range from asymptomatic myocarditis to neurogenic stunned myocardium and heart failure. These effects are mainly due to activation of the sympathetic nervous system and catecholamine-associated myocardial injury.[71]

Acute coronary syndrome :

Published literature showed evidence of acute coronary syndromes, including ST-segment elevation myocardial infarction during therapy for the GBS with intravenous immunoglobulins,probably related to catecholamine surge.[72]

Electrocardiographic changes:

The electrocardiographic changes do not constitute specific pathology. A wide spectrum of electrocardiographic changes have been demonstrated, including giant T waves, prolonged QT intervals, ST-T changes, U waves, and atrio ventricular blocks,in addition to bradycardia[73] . These changes are believed to be secondary to associated myocardial involvement. Hence, patients manifesting with bizarre electrocardiographic results should be investigated for underlying cardiomyopathy.

Bladder and Bowel Dysfunction:

Different degree of Genitourinary system involvement is seen patients with GBS.. Urinary retention occurred in 8/ 30 patients' in Lichtenfelds series (30%), 14 of 127 (1 1 %)

patients reported by Ravn from Denmark and 27% of the MGH series. Ravn reported 2 of 127 patients had urinary incontinence [74] .4 cases (2%) in MGH series had overflow incontinence, 3 patients had motor paralytic bladders, and 1 had impaired bladder sensation[52]. Wheeler et al. reported 3 patients with detrusor areflexia, a positive bethanechol super sensitivity test and electromyographic evidence of neuropathy involving perineal muscles.[75]Constipation are noted in 14% of the MGH series. Fecal incontinence are reported in two patients of MGH series and 6 patients of Ravn series [59,74]

Sweating abnormalities: The presence of anhidrosis in some GBS patient showed impaired sympathetic output and was reported in 7 patients by the Tuck and McLeod series of patients.[7] Hyperhidrosis has also been identified in other series, as has been anhidrosis. Lichtenfeld also describes episodes of facial flushing,chest tightening, and bradycardia attributed to parasympathetic overactivity[59.]

Sympathetic skin response(SSR) :

SSR is a test of sudomotor function and represents the changes in potential recorded from the surface of skin following various internal or external stimuli. It is a non invasive methods and can be used to assess the integrity of the sympathetic sudomotor.SSR is a polysynaptic reflex that is activated by a variety of afferent inputs. The efferent part of reflex arch consisted of myelinated sympathetic fibers of neurons from intermediolateral nucleus in T1 to L2 part of spinal cord that terminate in paravertebral sympathetic ganglia. The post ganglionic fibers are non myelinated (type C fiber) and innervate the eccrine sweat gland. So,the effector of reflex arch and most probably generator of potential change are activated eccrine sweat glands with cholinergic mediation. The reflex is coordinated in the posterior hypothalamus, upper brain-stem reticular formation and spinal cord. Thus, central or peripheral lesions of the sudomotor system can impair the SSR, but most frequently used in

diagnosing the functional impairment of non myelinated post ganglionic sudomotor sympathetic fiber in peripheral neuropathy.

Methods of SSR :

The methods of SSR recording was first introduced in electrophysiological laboratory by Shahani in 1984.SSR may be elicited either directly or reflexly.The direct response is obtained by stimulating a peripheral nerve but not used in clinical practice frequently due to high threshold of sympathetic trunk for activation of unmyelinated C fibers and simultaneous activation of pain fibres.The other methods commonly used in practice are deep inspiration ,coughing or starling sound as described by S*hahan*i et al.

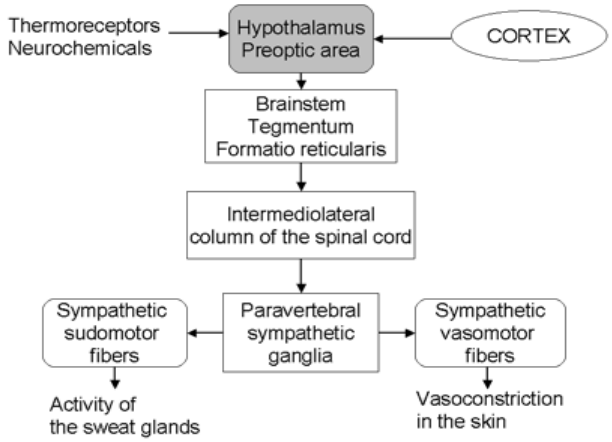


Figure1: Showing Neural components of the thermoregulatory system.

Technique of SSR:

The recording of SSR is being done at normal ambient temperatures, relaxed state, without acoustic disturbances . The standard surface Ag-Ag Cl electrodes are used for recording and are placed on the palm (active) and referenced against the volar forearm or dorsum of the hand,and on the sole of the foot (active) and referenced against the shin or dorsum of the foot.The ground electrode is proximal to the recording electrodes. Simultaneous bilateral recording from upper and lower extremities is recommended.

The study of SSR used an EMG machine with filter setting of low frequency at 0.2HZ and high frequency at 500HZ and sweep speed at 1 second per division.

The SSR can be evaluated either qualitatively or quantitively. In clinical practice qualitative evaluation is preferred and accept only absence of SSR as a pathological. The quantitative evaluation using latency prolongation or reduction of amplitude as a parameters is used in some laboratories, but difficult to interpret the result due to the variation of results in different conditions' and different time in the same person.

There are only two studies available on SSR abnormalities in GBS. Taly AB et al[76] studied SSR abnormalities in 24 GBS patients of which nine had absent SSR.13/24 patients' were showing evidence of clinical dysautonomia, of whom five had absent SSR..Five patients of Taly series were showing features of predominant axonal damage with preserved SSR. Deniz and Yerdelen [77] studied 14 patients with GBS, among whom 13 had AIDP and one had AMAN.Out of 14 patients ,SSR could not be elicited in two patients including one AMAN but in the rest of the 12 patients ,amplitude of SSR was found to be decreased when compared with control subjects(P=0.004).Both these studies showed SSR abnormalities are common in GB syndrome and may be complementary to bed-side tests for autonomic dysfunction.

MATERIALS AND METHODS

Eight GBS patients admitted between July 2010 to March 2011 in the Department of Neurology, Christian medical college ,Vellore were recruited into the study after obtaining IRB Clearance and tests of autonomic function were performed on them.The test battery consisted of Resting heart rate and RR interval variability following deep breathing(RRIV) and on standing ,Resting BP and BP response to standing for three minutes and immersion in cold water , cardiac response to Valsalva maneuvers and SSR(sympathetic skin response) . The presence of fluctuation of pulse and BP over 24 hours, sweating abnormalities and bladder and bowel dysfunction were also recorded. The patient's disability at the time of testing were graded on a scale from 0 to 6 (Hughes functional grade) Status Criteria:

0	Normal
I	Minimal sign and Symptoms ,able to run
2	Ambulates independently
3	Moderate disability,able to walk 5 met with aid
4	Bed bound
5	Required assisted respiration
6	Dead

INCLUSION CRITERIA:

All patients at or above 18 years of age who satisfy the diagnostic criteria for typical Guillain Barre syndrome was included for the study.

Diagnostic criteria for typical Guillain Barre syndrome :- :-

Features required for diagnosis :

1.Progressive weakness in both arms and both legs

2. Areflexia

Features strongly supporting diagnosis :-

1.Progression of symptoms over days to four weeks

2. Relative symmetry of symptoms

3.Mild sensory symptoms or signs

4. Cranial nerve involvement especially bilateral weakness of facial muscles

5 .Recovery beginning 2- 4 weeks after progression ceases

6. Presence of autonomic dysfunction

7.Absence of fever at onset

8. High concentration of protein in cerebrospinal fluid with < 1 cells

Features casting doubt on the diagnosis :

1. Marked persistent asymmetry of weakness.

2. Persistent bladder or bowel dysfunction.

3. Bladder or bowel dysfunction at onset.

4 .More than 50 mononuclear leukocytes/mm3 in CSF.

5. Presence of polymorphonuclear leukocytes in CSF.

6. Sharp sensory level.

NEUROPHYSIOLOGICAL CRITERIA:-

I used modified Cornblath et al. criteria for electrophysiological diagnosis of GBS[78]

AIDP :At least one of the following in each of at least two nerves or at least two of the following in one nerve if all others inexcitable and d CMAP > 10 % LLN:

Motor conduction velocity < 90% LLN (85 % if d CMAP < 50 % LLN)

Distal motor latency > 110 % ULN (> 120 % if dCMAP < 100 % LLN)

pCMAP / dCMAP ratio < 0.5 and dCMAP > 20 % LLN

F-response latency > 120% ULN

AMSAN :-None of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP < 10 % LLN

Sensory action potential amplitudes < LLN

AMAN :-None of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP < 10 LLN

LLSensory action potential amplitudes normal

Inexcitable: dCMAP absent in all nerves or present in only one nerve with dCMAP <10% LLN

(dCMAP=compound muscle action potential amplitude after distal stimulation; pCMAP=compound muscle action potential amplitude after proximal stimulation; LLN=lower limit of normal. ULN=upper limit of normal.)

EXCLUSION CRITERIA :

1.Patients'having any symptoms suggestive of peripheral neuropathy before the development of GBS.

2.Comorbidities like Diabetes mellitus ,Hypertension ,Coronary artery or heart disease,Thyroid diseases

3) Human immunodeficiency virus infection

4) Collagen vascular disease

5) Neurotoxic drugs or toxin exposure

6) Porphyria or Alcoholism

as determined by a detailed history examinations and relevant tests',which may affect the autonomic nervous system or resting heart rate or blood pressure,were not included in this study.

Methods :

Autonomic function tests was carried out by using

1) Philips bed side ECG monitor

2) Pulse Oximeter

3)Sphygmomanometer

All the patients were closely observed for the symptoms and sign of autonomic dysfunction including continuous recording of heart rate and blood pressure using Philips bed side ECG monitor.All the data of resting HR and BP, trends of HR and BP over 24 hours and battery of autonomic function test conducted were retrieved once every 24 hours for the first three days of admission followed by once every week . The recording was continued until the first 4 weeks of illness or improvement by 1 functional grade (Hughe's grading), whichever was earlier.

Procedure of autonomic evaluation.

Resting HR:

Resting HR were recorded when the patient lies in supine position for ten minutes prior to the test.

Resting BP:

Resting systolic and diastolic blood pressure were recorded from brachial artery with the help of Mercury sphygmomanometer with cuff applied to the right or left arm.Tachycardia was defined as HR> 100 beat/min and bradycardia as HR<60 beat/min

Labile HR and BP:

Fluctuation of HR and BP(labile) were recorded with the help of continuous Philips bed side ECG monitor with setting of every 15 min during first three days of admission followed by every 30 minutes till the termination of studies..Fluctuation was considered significant (labile

HR and BP) when fluctuation of systolic BP was >40 mm Hg/day and HR >30 beat/min in a day.[79]

HR response to deep breathing/I-E Difference (I-E):

The patients were instructed to breathe deeply at a rate of 6 breaths/min in the sitting position. The maximum and minimum R-R intervals were measured during each breathing cycles and converted to beats per minute. The result was then expressed as mean of the difference between maximum and minimum heart rate for six measured cycles in beats per minute. Deep breathing difference(DBD/I-E differences)=mean of heart rate differences in 6 breath cycles and considered abnormal according to age dependent values.[80]

HR Response to active change of posture(30/15 RATIO):

The patient was observed for 5 minutes of quiet breathing, following which the patient was asked to stand up as quickly as possible,un aided . The ratio of the longest RR interval around the 30th beat after standing to shortest RR interval around 15th beat reflect 30/15 ratio.A ratio of 1.00 or less was defined as an abnormal response, 1.01-1.03 as borderline and 1.04 as normal response.[80]

HR variation to Valsalva Maneuver/ Valsalva ratio (VR).

After 30 minutes of rest in a lying position with 30 degree head-up tilt, the patient was asked to blow into a mouthpiece connected to a mercury sphygmomanometer and maintain a pressure of about 40 mmHg for 15 seconds. The ratio of the longest RR interval within 40 beats after the maneuver to the shortest RR interval during the maneuver will be taken and the maximum response of three successive maneuvers will be recorded. The heart rate changes induced by the Valsalva maneuver was expressed as the ratio of the maximal tachycardia during the maneuver to the maximal bradycardia after the maneuver.

This ratio was defined as the Valsalva ratio and was calculated as the ratio of maximum R-R interval after the maneuver to minimum R-R interval during the maneuver.

Valsalva ratio(VR)= maximal tachycardia/maximum bradycardia= maximum R-R interval/minimum R-R interval.

A value of 1.10 or less was defined as an abnormal response, 1.11-1.20 as borderline, and 1.21 or more as a normal response.[81]

Postural changes in systolic BP (where feasible):

The patient was asked to rest in a supine position for 5 minutes and the resting BP was recorded. The patient was then asked to stand unaided, and remain standing unsupported for 3 minutes. The difference between the resting and standing BP levels was calculated. The fall in systolic BP of 30 mm Hg or more was defined as abnormal, fall between 10-29 mm Hg as borderline and a fall less than 10 was considered normal.[82]

Hand immersion test:

After resting in a lying position for 5 minutes, one hand was immersed in Ice Cold water for 2 minutes or as long as the subject could tolerate. A rise of the diastolic blood of >15 mm Hg was considered normal, and values of 1 1 to 15 mm Hg as borderline.[82]

Sympathetic skin response test (SSR) :

SSR were done in all of our patients with the help of EMG machine (Nicolet Viking electro diagnostic system).Study were done in relaxed and awake state with skin temperature 24- 32^0c using EMG machine with filter setting of low frequency at 0.2HZ and high frequency at 500HZ and sweep speed at 1 second per division using deep inspiration for electrical stimulation.I used standard surface Ag-AgCl electrodes for recording and placed on the palm (active) and referenced against dorsum of the hand for upper limb and on the sole of the foot (active) and referenced against the dorsum of the foot for lower limbs. Simultaneous bilateral recording from upper and lower extremities was done . If deep

inspiration failed to elicit SSR in the first pass, a second attempt was made after a gap of 5 minutes to overcome habituation. A minimum of three attempts were made before declaring it as absent SSR. Failure to elicit SSR with deep inspiration even after 3 attempts was considered as abnormal test.

Sweating abnormalities: The symptoms and sign of sweating abnormalities were recorded including areas of anhidrosis, hyperhidrosis,episodic flushing,cold or warm to touch.

Bowel and bladder dysfunction: The symptoms and sign of bladder and bowel dysfunction were recorded with help of history and relevant clinical test .

Longitudinal Study of Autonomic Function:

The battery of Autonomic function test was performed once daily for first three days of admission,first preferably within 24 hours followed by once every weeks . The recording was continued till first 4 weeks of illness or improvement by 1 functional grade (Hughe's grading), whichever was earlier. To exclude major circadian variations, the procedures were always done between 10.00 and 16.00 hours.

STATISTICAL METHODS

Statistical analyses were performed with SPSS (windows 11.5 version, SPSS inc, Chicago), for all variables and descriptive statistics were calculated .Data were expressed as mean $\pm$ SD unless indicated otherwise. The analysis and comparisons of clinical characteristics were done by chi-square test. The differences between disease stages were analyzed by two tailed unpaired t test. Results were considered statistically significant for p value of < 0.05.

RESULTS

Patient's clinical and biological characteristics

After applying the inclusion and exclusion criteria, a total of 8 patients were included for longitudinally performed autonomic function tests (ATs). This comprises 5 (62.5%)males and 3(37.5%) females. The mean age of these patient were 35.37 ± 15.20 years (range, 18-60 years).The mean Hughes disability score(DS) at admission was 3.75 (range, 2-5; median 4).The mean duration of illness at the time of presentation was 3.75 ±2.05 days where as mean duration of the progressive phase(onset to nadir) was 9.37 ±6.09 days, ranges from <36 hours to 20 days. Out of the eight patients, 7 had AIDP and remaining one patient had AMAN.Two patients (25%) had required mechanical ventilation. Mechanical ventilation was started on the day of admission (2^{nd} day of illness) in one patient and was required for 3 weeks where as in other patient it was started on 6^{th} day of admission (9^{th} day of illness) and continued for 100 days. All the patients of study group were taken for plasma exchange and variable number and amounts of exchanges were done (Minimum 3.5L/4 cycle and Maximum 8L/8 Cycles) but in one patient (patient 3), IVIG was given following intolerance to PE

.Antecedent Events: Out of eight patients, two had history of myalgia and fever , 2 had history of diarrhea and one had history URTI an interval ranging from 10 to 21 days prior to onset of illness .

Cranial Nerve Involvement: Six patients had bifacial weakness,4 bulbar weakness along with bifacial weakness, none having ophthalmoplegia or isolated bulbar involvement.

Sensory symptoms or sign: History of painful sensory paresthesia of limbs was obtained in 6 patients.One patient was detected to have a stocking pattern of sensory loss

CSF studies:CSF study was done in all patient, usually within 24 hour of admission. Out of 8 patient, 6 had a CSF protein of>45mg/dl with albumin cytological dissociation.

Figure2. Showing distribution of age

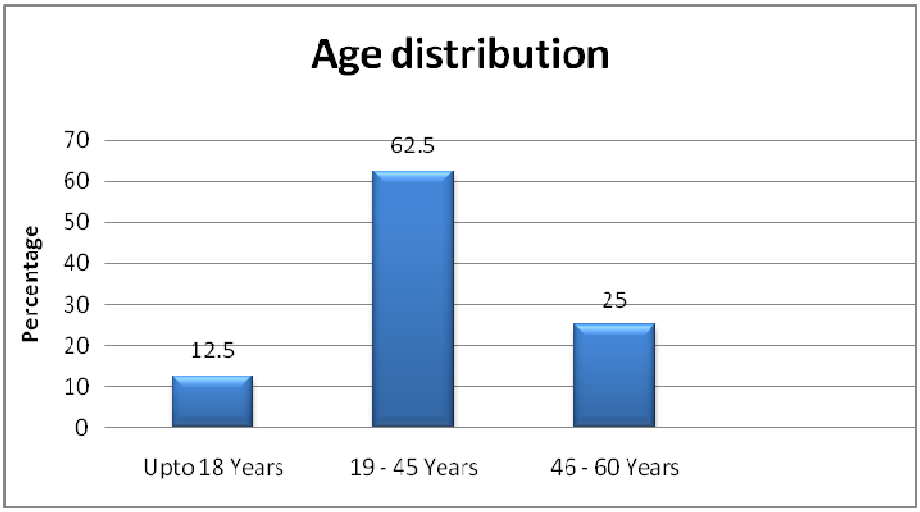


Figure 3.Showing time required to reach onset to nadir

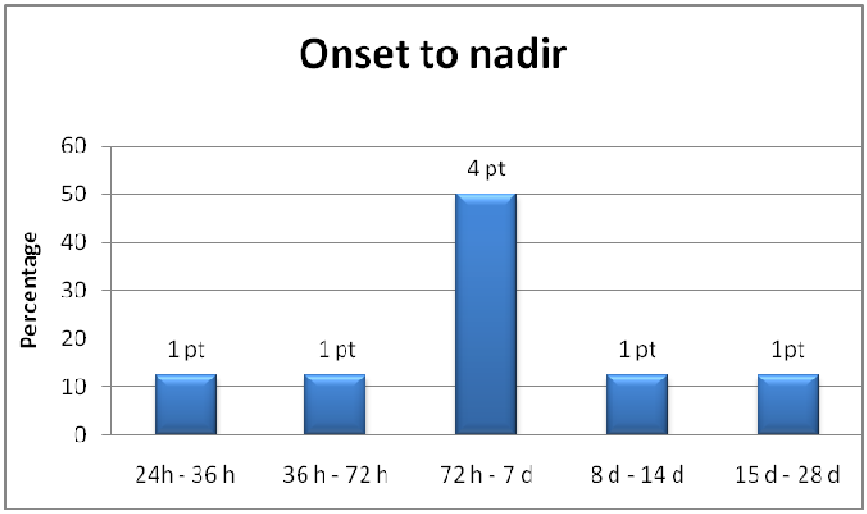


Figure 4. Showing Hughes functional grade at admission & discharge/ termination of study

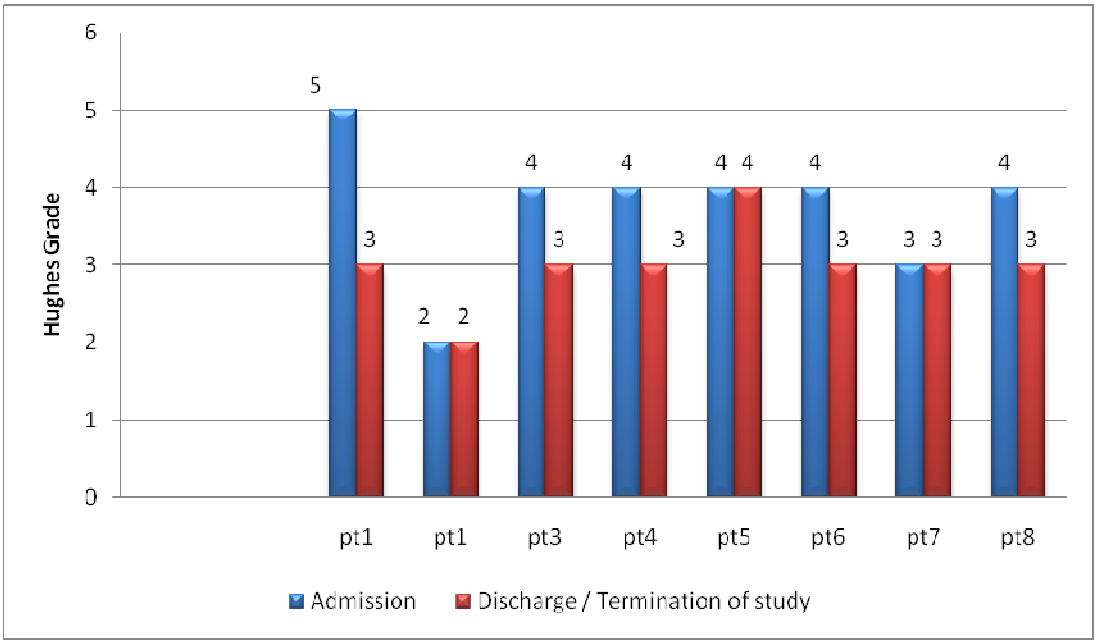


Table.1 Showing duration of illness at presentation

Duration	Frequency	percent
24 h-36h	2	25
36h-72h	2	25
72h-7d	3	37.5
8 d-14 d	1	12.5

Table 2.Showing clinical characteristics of patients

Characteristics	Minimum	Maximum	Mean	SD
Age	18	60	35.50	15.20
Days of illness at presentation	2	8	3.75	2.05
Disability score at presentation	2	5	3.75	0.88
Disability score at discharge/termination of study	2	5	3.12	0.83
Onset to nadir in days	1	20	9.37	6.09

Table 3. Showing antecedent Events

Events	Frequency	Percent
Diarrhea	2	25
Fever and Myalgia	2	25
URTI	1	12.5
Nil	3	37.5

Table 4 Showing cranial nerve involvement

Cranial nerve	frequency	Percent
Bifacial involvement	6	75
Bulbar involvement	4	50
Nil	2	25

Table 5.Showing sensory symptoms/sign

	Frequency	Percent
Painful paresthesia	6	62.5
Sensory loss	1	12.5
Nil	2	25

Symptoms and clinical sign of autonomic dysfunction

During the study period, a history of symptoms of autonomic dysfunction was noted,clinical cardiovascular manifestation of autonomic dysfunction was recorded and battery of autonomic function test were performed . Due to mechanical ventilation, motor disability, or facial or bulbar paresis, the complete battery of autonomic function test could not be applied to every patient. 7/8 patients (87.5%) had evidence of dysautonomia of variable severity during the course of their illness.

Symptoms of autonomic dysfunction:

Postural dizziness was reported in two patients. In one patient postural dizziness preceded the onset of motor weakness by 5 days and this symptom was very prominent and persisted upto 10 weeks after the onset of neuropathy inspite of improving motor weakness.The bowel dysfunction was observed in 4/ 8 patients, 3 had history of constipation where as one had both constipation and urinary retention..One patient had history of constipation 3 days preceding the motor weakness where as one had urinary hesitancy 1 day prior to onset of

motor weakness.The sweating abnormalities was detected in 3 patients.Two patients were showing anhidrosis of both lower limbs below knee joints where as in one patient anhidrosis of both lower limbs below ankle joint was seen during first 2 weeks followed by episodes of hyperhidrosis of different part of body including both lower limbs,trunk and face and persisted upto 4th weeks of illness. Palpitation and increased thirst were seen in one patient.

Table 6 Showing symptoms of autonomic dysfunction :

symptoms	Frequency	Percent
Constipation	4	50
Anhidrosis	3	37.5
Postural dizziness	2	25
Palpitation	1	12.5
Increased thirst	1	12.5
Urinary retention	1	12.5
Hyperhidrosis	1	12.5
Nil	2	25

Table7. Showing symptoms of dysautonomia before onset of motor weakness

Symptoms	Number	Percent	Cumulative percent
Dizziness	1	12.5	12.5
Constipation	1	12.5	25
Urinary hesitancy	1	12.5	37.5
Nil	5	62.5	100

Table 8. Showing bladder and bowel dysfunction:

	Frequency	Percent
Bowel dysfunction (constipation)	4	50
Bowel (constipation) & bladder dysfunction (retention)	1	12.5
Nil	4	50

Table 9.Showing sweating abnormalities

	Frequency	Percent
Nil	5	62.5
Anhidrosis of lower limb	3	37.5
Episodic hyperhidrosis	1	12.5

Clinical cardiovascular manifestation of autonomic dysfunction

Sinus tachycardia:

Sinus tachycardia was most common abnormality and was detected in seven of 8 patients'(87.5%) The heart rate of eight patients' ranged from 50-152 beat/min .Tachycardia persisted for 2 weeks in one patient,3 weeks in 5 patients and upto 4th weeks in one patient.

Sinus bradycardia:

Three patients' had episodes of sinus bradycardia which lasted for 1 Week in one patient and for two weeks in 2 patient.

Labile HR:

High diurnal variation of HR(>30 beat/min) was observed in 75% of patients.The maximum fluctuation of HR in a single day was recorded 102.Labile HR persisted for 1 week in one patient,2 weeks in one patient ,3 weeks in three patient and upto termination of study (4^{th} week) in one patient.

Hypertension:

Hyprtension of variable severity was detected in 6 patient,none of whom were known to be hypertensive prior to this illness .It persisted for 1 week in one patient ,2 weeks in 3 patients ,where as in other two patients upto 3^{rd}weeks. The hypertension was persistent in 5 patients and paroxysmal in one patient. The maximum systolic and diastolic BP recorded in our patient was 200 mmHg and 152 mmHg respectively.None of our patients having evidence of persistent of severe hypertension or hypertensive crisis as reported earlier and not treated except one patient as beta blocker and antihypertensive might aggravate incipient hypotension and bradycardia. One patient was treated with low dose of beta blocker and tolerated well without significant fall of BP and HR.

Hypotension:

The episodes of hypotension was observed in four patients and persisted upto 2nd week of illness. Hypotension was spontaneous in three of 4 patients' ,usually preceded by highly labile blood pressure. Although spontaneous hypotension was not observed in one patient,but she had hypotensive episodes during plasma exchanges and on active change of posture .In other two patients having evidence of hypotensive episodes both spontaneously and during plasma exchanges.The minimum systolic and diastolic Blood pressure recorded in our patient was 54 mmHg and 40 mmHg respectively.

Labile BP:

High diurnal variation of blood pressure(>40 mmHg within single day) was observed in 6 patient. The maximum fluctuation of systolic BP recorded in single day was 144 mmHg .

Fluctuation of HR and BP during PE:

The significant fluctuation of HR and BP was observed in four of 8 patient who received PE.The most common type of abnormalities detected was episodes of tachycardia and hypotension requiring frequent IV fluid challenge and termination of procedure .In one patient, as the episodes of hypotension was very frequent and severe, PE was discontinued and IV Ig was started.

Figure 5.Showing clinical cardiovascular manifestation of autonomic dysfunction

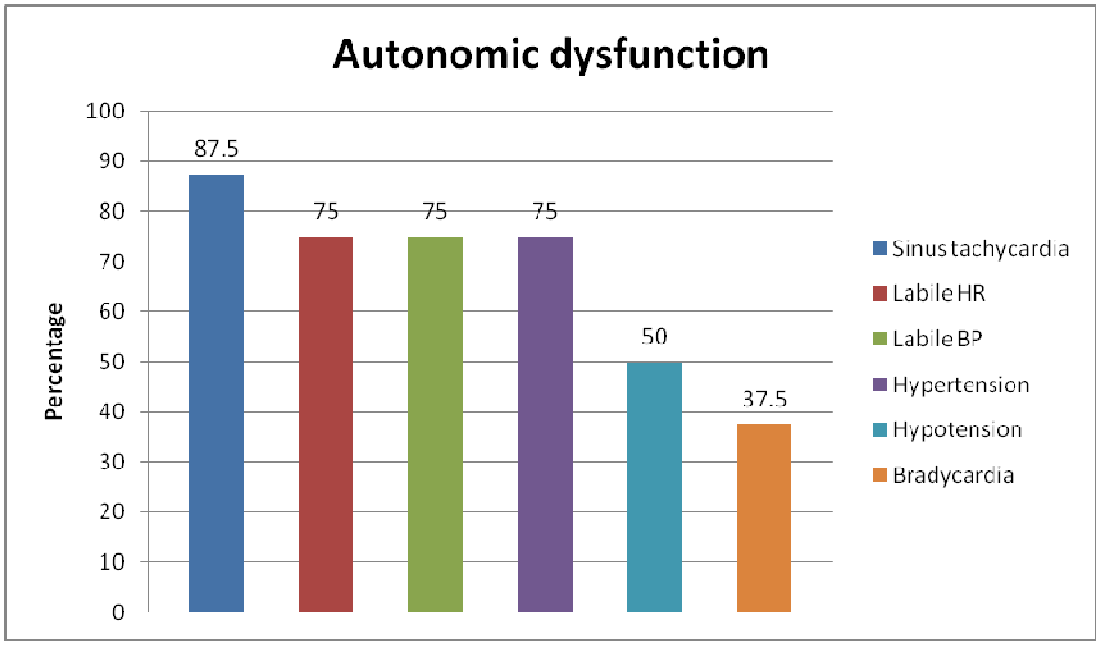


Table 10 Showing fluctuation of HR and BP during PE:

	Frequency	Percent
Significant fluctuation of HR & BP	4	50
Hypotensive episode	3	37.5
Needs termination of procedure	3	37.5
Discontinuation of PE	1	12.5
Nil	4	50

Table 11.Showing clinical cardiovascular manifestation of autonomic dysfunction.Mean(maximum-minimum)

Pt number	Mean Resting HR	Mean fluctuation of HR	Mean systolic BP	Mean fluctuation of systolic BP
1	113 (86-130)	69(54-90)	150.3(122- 166)	52.8(7-78)
2*	91.2(74-110)	24.4(20-30)	100.8(90-108)	20.8(14-26)
3	110.6 (92-130)	48.1 (18-68)	157.6(140-188)	81.66(49-146)
4	112(104-120)	52.2(38-62)	145.6(128-170)	44(30-80)
5	102(76-114)	45.6 (22-62)	149.6(120-170)	62.66(22-100)
6**	90(78-100)	21.6(14-30)	118.4(110-126)	27(18-34)
7	114(108-120)	41(24-70)	150(134-162)	58.6(20-101)
8	113.6 (92-136)	53.6(34-80	148.8(110-166)	48.4(20-64)

*Although, clinical cardiovascular sign of dysautonomia was absent in this patient but she had significant symptoms of postural dizziness, hypotensive episodes during PE and on standing and presence of abnormalities on bed side cardiovascular autonomic function test.

*Patient not having autonomic dysfunction

Table 12 Showing trends of clinical cardiovascular function(mean)

	1st week (n=7)	2nd week(n=8)	3rd week(n=8)	4th week(n=4)
Resting HR	112.33(8.54)	114.57(16.27)	98.28(12.51)	91(14.28))
Fluctuation of HR over 24 hs	54.66(16.90)	52.14(18.47)	36.57(11.29)	32.25(19.05)
Systolic BP	147(24.74)	142(18.72)	133.42(24.91)	131.50(7.54)
Diastolic BP	91.66(18.04)	96.57(21.56)	79.42(8.38)	77(11.37)
Fluctuation of SBP over 24 hs	60(28.92)	51.57(18.79)	40.57(25.63)	35.75(17.85)

Figure 6. Showing mean resting HR

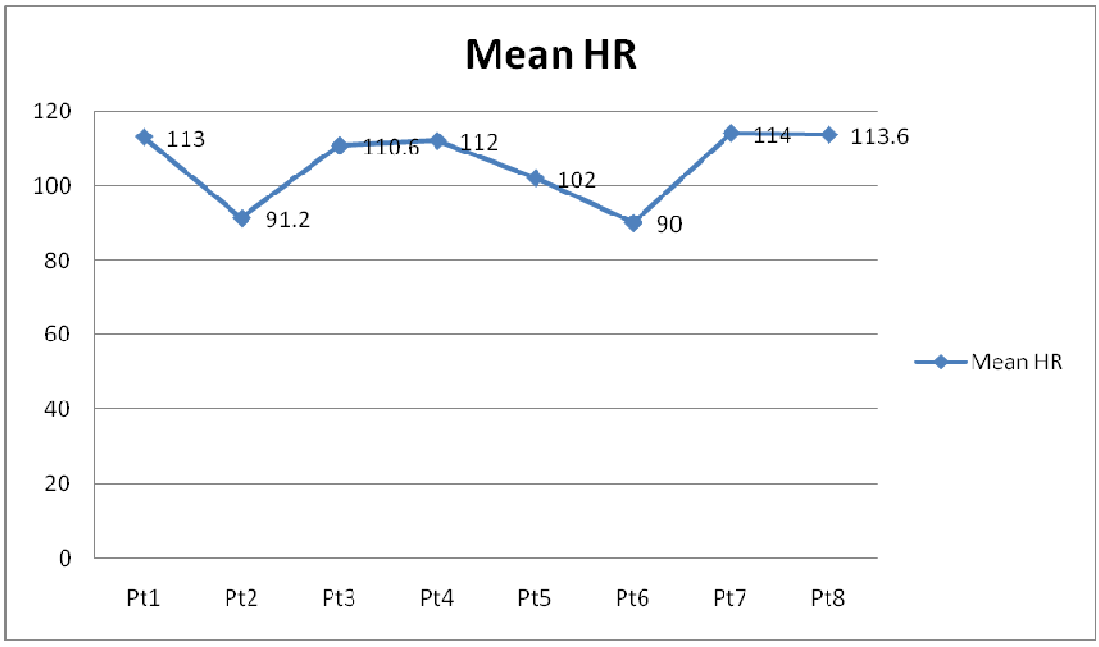


Figure 7.Showing mean fluctuation of HR

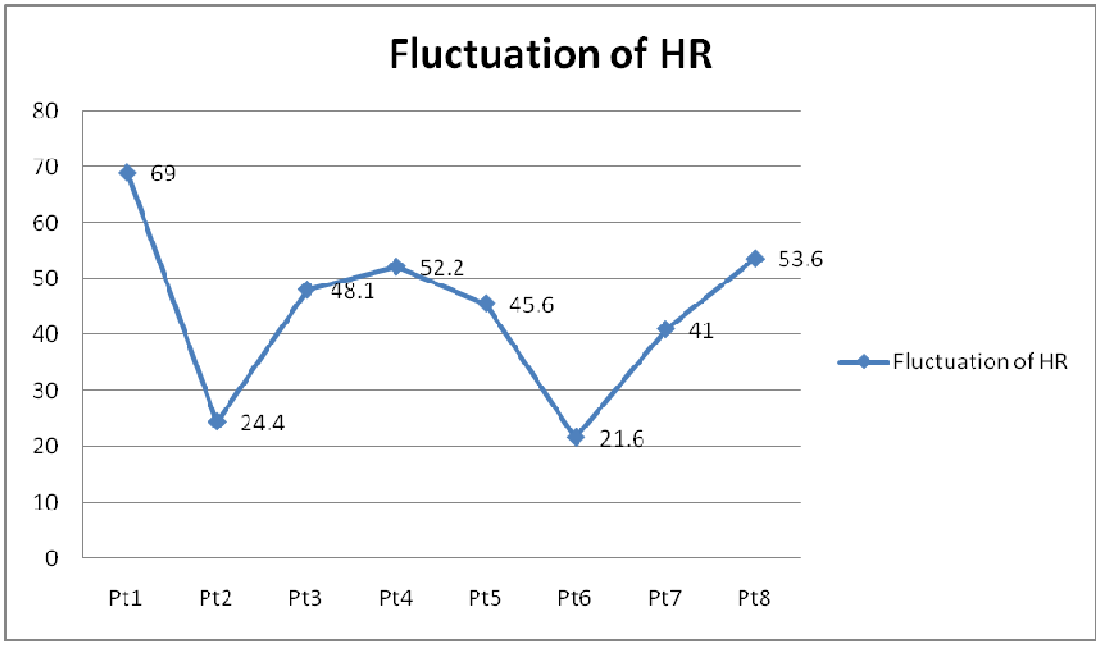


Figure 8.Showing mean systolic BP

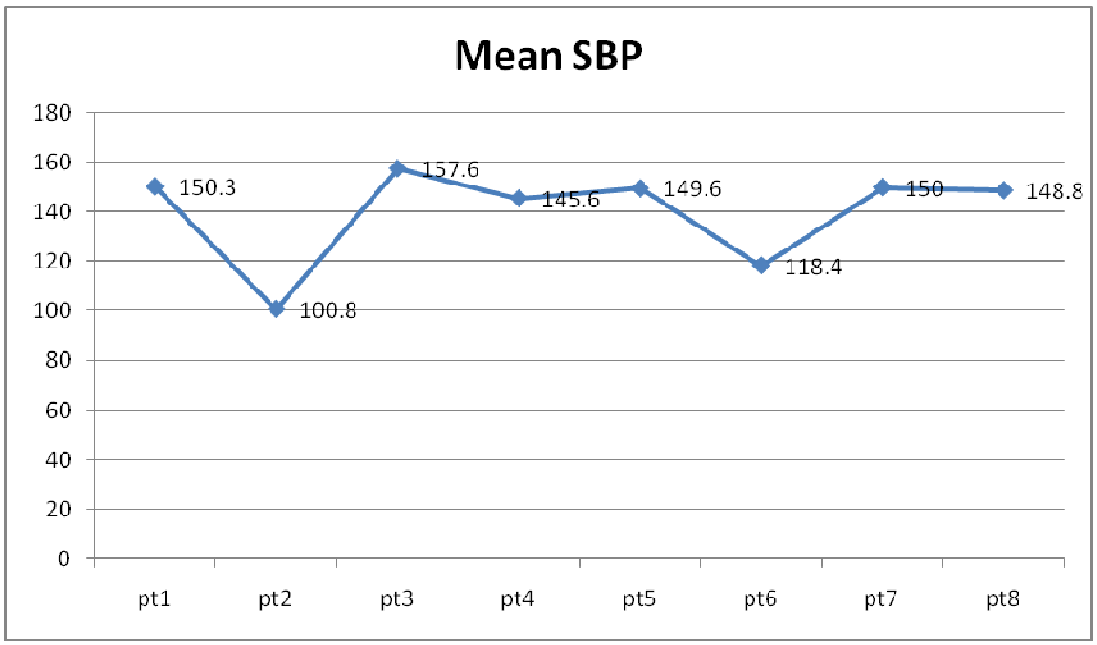


Figure 9 Showing mean fluctuation of systolic BP

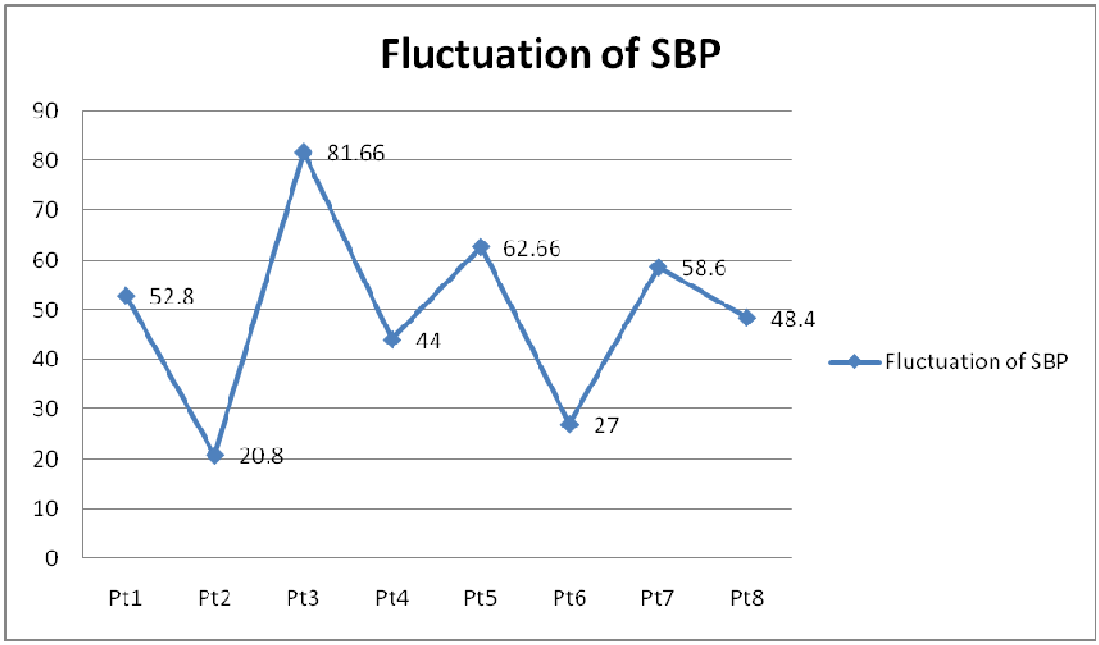


Figure 10. Showing trends of clinical cardiovascular function in patients with dysautonomia

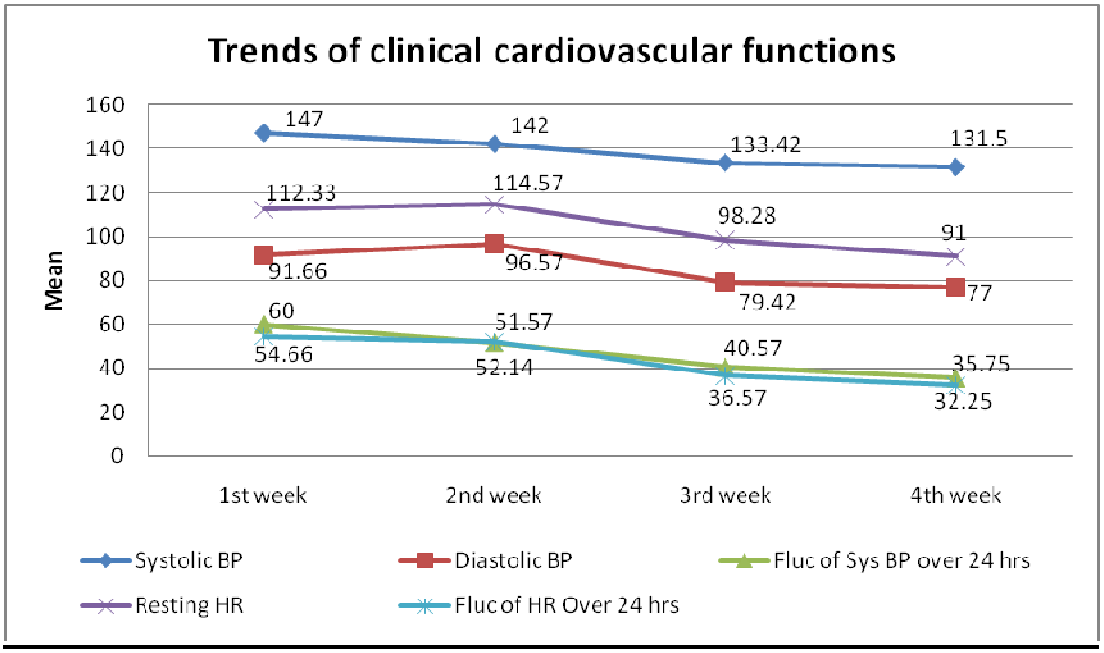


Table 13 showing Cardiovascular manifestation of autonomic dysfunction

Abnormalities	N	percent
1) Rhythm abnormalities		
Sinus tachycardia-	7	87.5
Bradycardia	3	37.5
-Labile HR	6	75
2)BP variability		
-Hypertension	6	75
-Hypotension	4	50
-Labile hypertension	6	75
3)ECG changes		
ST change	2	25

Table 14. Showing bed side Autonomic function test

Autonomic function test	Number of patient test done	Criteria of abnormality	Number of pt with abnormal response			% of abnormal response
			Abnormal	Border line abn.	Total	
HR response Response to deep breathing (I -E differences)	6	-Age dependent values	3	0	3	50
- 30/15 ratio on Standing	4	-Abnormal ≤ 1.01 -Borderline abnormal= 1.01-1.03	1	1	2	50

- Valsalva ratio	2	-Abnormal ≤ 1.10 -Borderline abnormal= 1.11-1.20	1	0	1	50
BP response -Rise of diastolic BP in cold immersion test	8	-Abnormal≤ 10 mm Hg rise of diastolic BP -Border line abnormal =11-15mmHg rise of diastolic BP	3	2	5	62.5
-Change of systolic BP on standing upto 3 min.	4	-Abnormal= Fall of systolic BP by l≥ 30 mmHg -Borderline abnormal= Fall of systolic BP between 10-29 mmHg	1	1	2	50

Table 15.Bed side autonomic function test (worst result of each patient on longitudinal study)

Patient Number ➢	1	2	3	4	5	6	7	8
30:15 ratio	ND	1	ND	ND	ND	0	2	0
E:I ratio	ND	0	2	2	ND	0	2	0
Valsalva ratio	ND	0	2	ND	ND	ND	ND	ND
Fall of systolic BP on standing	ND	2	ND	ND	ND	0	0	1
Cold immersion test	2	2	2	1	0	0	0	1

Not done= ND,Normal=0,border line abnormal =1,abnormal =2

Table 16 Showing Sympathetic skin response test (SSR) :

	Frequency	Percent
Absent	5	62.5
Present	3	37.5
Total	8	100

Normalized Total Autonomic Score (NTAS)

On the basis of history,clinical cardiovascular sign of autonomic dysfunction,cardiovascular autonomic function test (testing both sympathetic and parasympathetic arm of ANS), presence or absence of bladder,bowel and sudomotor dysfunction a normalized total autonomic score (NTAS) was obtained by scoring each variable of autonomic dysfunction as below.

Variables	Score
1) Symptoms of autonomic dysfunction	Nil =0, Yes =1
2) Clinical sign of autonomic dysfunction	
Resting HR	Normal=0,tachycardia or bradycardia =1, Both tachycardia and bradycardia =2
Fluctuation of HR Over 24 hs	Normal =0, Yes =1
Resting BP	Normal=0,hypertension/hypotension =1 Both hypertension and hypotension =2

Fluctuation of systolic BP over 24 hrs Normal =0, Yes =1

Fluctuation of HR and BP during PE Normal=0, Yes =1

(Hypotension/ hypertension/tachycardia/bradycardia)

Intolerance to PE(Discontinuation of PE)=2

1) Test of Parasympathetic function

30:15 ratio Normal or not done =0,border line abn =1,abn.=2

I-E differences. Normal or not done =0, borderline abn.=1abn.=2

Valsalva ratio Normal or not done =0,border line abn =1,abn.=2

2) Test of Sympathetic function

Fall of systolic BP on standing Normal or not done =0,border line abn =1,abn.=2

Cold immersion test Normal or not done =0,border line abn =1,abn.=2

3) Bladder & bowel dysfunction

Bladder or Bowel dysfunction Nil =0, yes =1

Both Bladder & Bowel dysfunction =2

6) Sudomotor dysfunction

Sweating abnormality Nil =0, Yes =1

SSR test Normal =0, Yes =1

Both sweating and SSR abnormalities = 2

4) ECG changes NO=0,yes=1

Maximum score = 24

These score were added together for each patient and normalized to a 24 point normalized autonomic score where one or more autonomic function test could not be performed.

Table 17 .Showing Suggested Normalized total Autonomic score (NTAS) classifying degree of dysautonomia

Degree of dysautonomia	Normalized autonomic score
Mild dysautonomia	<10
Moderate dysautonomia	10-16
Severe dysautonomia	>16

Table 18.Showing Normalized total autonomic score (NTAS) in the 1st week of illness

Patient Number ➢	1	2	3	4	5	6	8
Autonomic symptoms	0	1	0	0	1	0	0
Resting HR	2	1	2	2	1	0	1
Resting BP	2	0	2	1	2	0	1
Fluctuation of HR Over 24 hs	1	0	1	1	1	0	1
Fluctuation of systolic BP over 24 hs	1	0	1	1	1	0	1
Fluctuation of HR and BP during PE	0	1	2	0	0	0	0
30:15 ratio	ND	1	ND	ND	ND	ND	ND
I-E differences	ND	0	2	2	ND	0	0

Valsalva ratio	ND	O	2	ND	ND	ND	ND
Fall of SBP on standing upto 3 min.	ND	2	ND	ND	ND	ND	ND
Cold immersion test	2	2	2	1	0	0	0
Bladder &Bowel dysfunction	0	0	0	2	1	0	1
Sudomotor dysfunction	1	0	1	2	0	0	0
ECG changes	0	0	1	1	0	0	0
Total	9	8	16	13	7	0	5
Normalized total Autonomic score(NTAS)	13.5	8	19.2	17.33	10.5	NA	6.6

Table 19.Showing Normalized total autonomic score (NTAS) in 2nd week of illness

Patient Number ➢	1	2	3	4	5	6	7	8
Autonomic symptoms	0	1	0	0	0	0	1	0
Resting HR	2	0	1	2	1	0	1	1
Resting BP	1	0	1	1	1	0	1	0
Fluctuation of HR Over 24 hours	1	0	1	1	1	0	0	1
Fluctuationof SBP over 24 hours	1	0	1	0	0	0	0	1
Fluctuation of HR and BP during PE	0	0	ND	0	1	0	1	0
30:15 ratio	ND	1	ND	ND	ND	0	2	ND
I-E differences	ND	0	2	ND	ND	0	2	0

Valsalva ratio	ND	0	2	ND	ND	ND	ND	ND
Fall of SBP on standing upto 3 min.	ND	2	ND	ND	ND	0	ND	ND
Cold immersion test	2	2	2	1	0	0	0	1
Bladder &Bowel dysfunction	1	0	0	2	0	0	0	1
Sudomotor dysfunction	1	0	1	2	0	0	1	1
ECG changes	0	0	1	0	0	0	0	0
Total	9	9	12	10	4	0	9	6
Normalized total autonomic (score(NTAS)	13.5	6.26	16	13.33	6	0	10.8	7.5

Table 20.Showing Normalized total autonomic score (NTAS) in 3rd week of illness

Patient Number ➢	1	2	3	4	5	6	7	8
Autonomic symptoms	0	1	1	0	0	0	1	0
Resting HR	1	0	1	1	1	0	1	0
Resting BP	1	0	0	1	0	0	1	0
Fluctuation of HR Over 24 hrs	1	0	1	1	0	0	0	1
Fluctuation of systolic BP over 24 hs	1	0	1	0	0	0	0	0
Fluctuation of HR and BP during PE	0	0	0	0	0	0	0	0
30:15 ratio	ND	0	ND	ND	ND	0	1	0
I-E differences	ND	0	2	1	ND	0	2	0
Valsalva ratio	ND	0	1	ND	ND	ND	ND	ND

Fall of SBP on standing upto 3 min.	ND	2	ND	ND	ND	0	0	1
Cold immersion test	1	2	2	1	0	0	0	1
Bladder &Bowel dysfunction	0	0	0	0	0	0	0	0
Sudomotor dysfunction	1	0	1	1	0	0	1	1
ECG changes	0	0	1	0	0	0	0	0
Total	6	6	11	6	1	0	7	4
Normalized total autonomic score(NTAS)	10.2	6	14.66	8	1.71	0	8.4	4.4

Table 21.Showing Normalized total autonomic score (NTAS) in 4th week of illness

Patient Number ➢	1	3	5	7
Autonomic symptoms	0	0	0	1
Resting HR	1	0	0	1
Resting BP	0	0	0	0
Fluctuation of HR Over 24 hs	1	0	0	0
Fluctuation of systolic BP over 24 hs	0	1	0	0
Fluctuation of HR and BP during PE	0	0	0	0
30:15 ratio	ND	ND	ND	1
I-E differences	1	ND	0	1
Valsalva ratio	ND	1	ND	ND

Fall of SBP on standing upto 3 min.	ND	ND	ND	0
Cold immersion test	0	1	0	0
Bladder &Bowel dysfunction	0	0	0	0
Sudomotor dysfunction	2	1	1	1
ECG changes	0	1	0	0
Total	5	6	1	5
Normalized total autonomic score	6	8	1.71	6

Table 22.Showing trends of Normalized Total Autonomic Score in weeks

Pt Number	Ist week	2nd week	3rd week	4th week
1	13.5	13.5	10.2	6
2	8	6.26	6	NA
3	19.2	16	14.66	8
4	17.33	13.33	8	NA
5	10.5	6	1.71	1.71
7	NA	10.8	8.4	6
8	6.6	7.5	4.4	NA

Figure 11. Showing trends of Normalized Total Autonomic Score in weeks

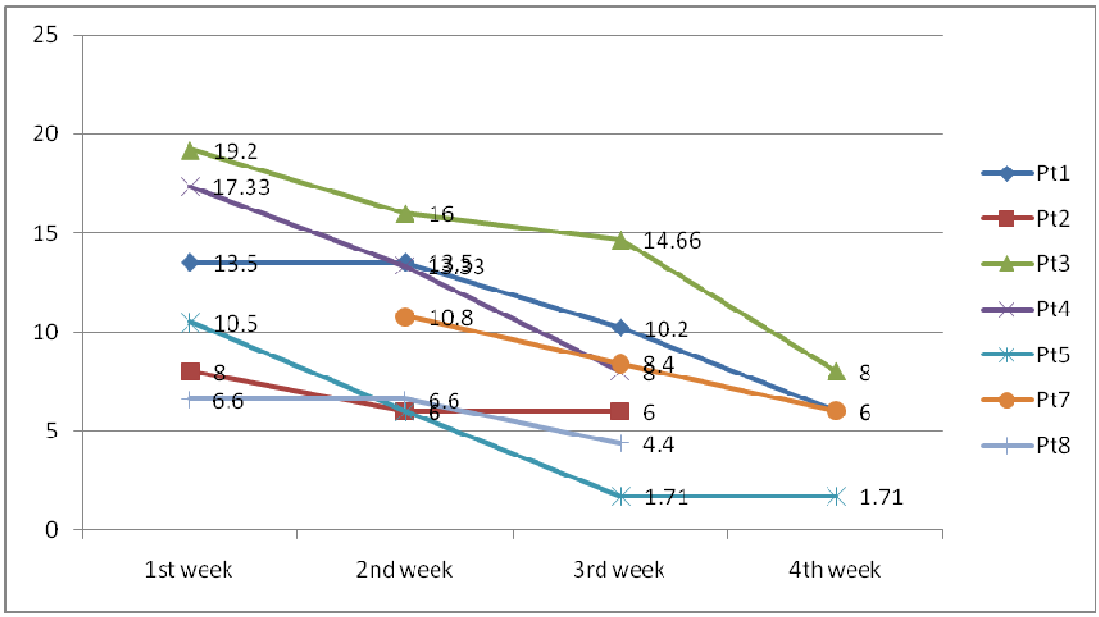


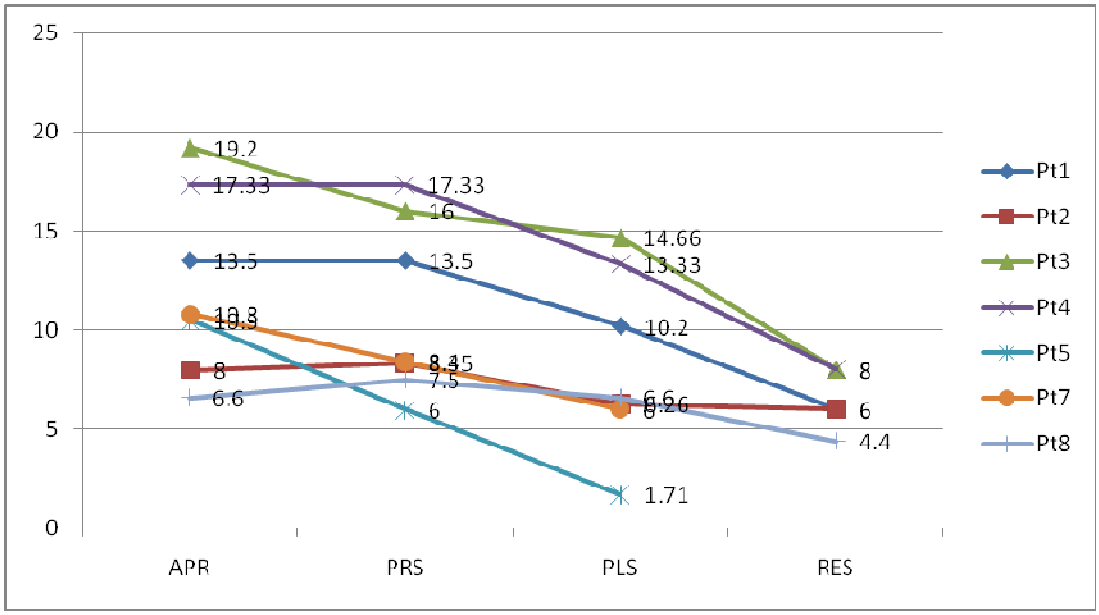
Table 23 Showing Normalized total autonomic score in different stages of patient with autonomic dysfunction

Pt number	At presentation	Progressive stage	Plateau stage	Remission stage
1	13.5	13.5	10.2	6
2	8	8.35	6.26	6
3	19.2	16	14.66	8
4	17.33	ND#	13.33	8
5	10.5	6	1.71	NA*
7	10.8	8.4	6	NA*
8	6.6	7.5	6.6	4.4

*All presented in progressive stage of the illness,two patients(5,7) was in plateau stage at the time of termination of study

#Attained nadir within 72 hrs. of illness

Figure 12. Showing NTAS different stages of patient with autonomic dysfunction



APR=At presentation,PRS=progressive stage,PLS=plateau stage,RES =Remission stage

Table 24. Showing Comparison autonomic dysfunction in GBS with available studies

Variable	Tuck and Mcleod [7]	Flachenecker et al[2]	Bansal et al[69]	Singh et al [68]	Asahina et al [3]	Present study
Number of patients	7	13	15	24	15	8
Age(Mean)	43±9 ys	52.5 ys (29-70 ys)	28.9 ±9.9ys	12-65 ys	37.1+16.2ys	35.37±15.2ys
Spectrum of patients	AIDP	AIDP	AIDP	AIDP	13AIDP 1AMAN	7AIDP 1AMAN
Incidence of Autonomic dysfunction	85.7%	69%*	67.7%	66.7%		87.5%
Duration of Illness at Presentation (Mean)	26 day	<14 days	?	?	6.5±3.7days	3.75±2.05days
Functional grade at presentation(Mean)	3.4	3.5	?	?	3.4±0.9	3.75
Mechanical ventilation	Nil	23.08%	20%	Nil	1/15	25%
Mortality	Nil	Nil	13.33%	8.33%	Nil	Nil
-Bladder dysfunction	-	-	0	20.8%	1/15	12.5%
-Bowel dysfunction	-	-	0	0	0	50%
- Sweating abnormalities	6/7(85.71%)	-	26.67%	12.5%	3AIDP 1AMAN	37.5% AIDP
Tachycardia	2/7(28.57%)	-	46.67%	33.3%	28.57%AIDP	75%
Bradycardia	0	-	0	8.3%	-	37.5%
Fluctuation of HR	0	-	-	-	--	75%
Hypertension	4/7(57.14%)	-	33.33%	20.8%	-	75%
Hypotension	0	+	0	-	-	50%
Fluctuation of BP	1/7(14.29%)	+	-	-	-	75%
E-I differences	-	+	-	30%	-	3/6 (50%)

30:15 ratio	-	+	-	35%	-	2/4(50%)
Valsalva ratio	-	+	4/9(44.44%)	28.6%	-	1/2(50%)
Cold immersion test	2/3(66.77%)	-	40%	36.6%	-	5/8(62.5%)
Tilt table/PCBP	3/7(42.86%)	-	20%	35%	0	½(50%)
CV R-R	-	-	-	-	1(AIDP)	-
SSR	-	-	-	-	-	4 AIDP/1AMAN (62.5%)
SSwR	-	-	-	-	Absent in 3AIDP 2AMAN	-
EEG changes	-	-	-	33.33%	-	25%
Plasma Noradrenalin	-	-	-	-	Increased 3AIDP 1AMAN	-
Pharmacological test						
Baroreceptor HR reflex test using phenylephrin	+(57.14%)	-	-	-	-	-
HR response to atropine	-	-	+ (46.67%	-	-	-

(- =Not done/not mentioned, + Abnormal ,CV R-R=Coefficient of variation of R-R intervals, SSwR=sympathetic sweat response ,PCBP=Postural change of BP)

* >90 % subclinical sign of autonomic dysfunction

Table 25 Showing relations of autonomic dysfunction

Abnormalities	P value
Hyper acute onset of illness	0.375
High Hughes functional grade (4/5)	1.00
Older age(>45)	1.00
Mechanical ventilation used	1.00
Sensory abnormality	0.250
Cranial nerve abn.	1.00
SSR abn.	0.375

Table 27 Showing relations of severe autonomic dysfunction

Abnormalities	P value
Hyper acute onset	1.00
High Huges functional garde(4/5)	1.00
Older age(>45)	0.035
Mechanical ventilation used	1.00
Sensory abnormalities	1.00
Cranial nerve abn.	0.46
SSR abnormalities	0.46
Bradycardia	0.107

DISCUSSION

A total of eight patients underwent a longitudinally performed autonomic function tests (ATs). 7/8 patients' had AIDP and one patient had AMAN .They were closely observed for the symptoms and sign of autonomic dysfunction including continuous recording of HR and BP, cardiovascular response to autonomic function test and SSR to look for sudomotor function. The possibilities of hypoxemia,sepsis,pulmonary embolism,medication and electrolyte disturbances causing abnormalities were excluded before recording cardiovascular abnormalities in all these patients' during the study period. The incidence of autonomic dysfunction in GBS has been reported to vary considerably earlier[1,2,3,68,69]. The variable incidence may be due to differences in various techniques, extent of testing and the arms of autonomic nervous system studied. Most of the available studies on autonomic dysfunction in GBS were done in limited number of patients, mainly AIDP.Prospective study of Singh et al[69]showed evidence of autonomic dysfunction in 16/24 GBS patients (67.7%) and was similar to Bansal etal [69](66%) patients.Both studies were done on AIDP patients', but tested limited arms' of autonomic nervous systems once and functional grades',duration of illness and stages of the patients' at the time of study were not highlighted .Tuck andMcLeod study showed autonomic dysfunction in six of 7 AIDP studied.[7] Tuck et al did not include symptoms of autonomic dysfunction and included patients' even during the plateau stages of disease .The mean duration of illness in Tuck's study group was 26 days (7-63 days).Flachenecker et al studied cardiovascular functions in GBS quantitively and showed 69 % of clinical and more than 90 % of subclinical sign of autonomic dysfunction in 13 of AIDP[2] .Flachenecker et al tested autononomic function longitudinally upto I year of illness, but most of the patients included in this study were in the plateau stages' but had moderate to

severe grades' of disease..Lichtenfds[59] who reported 12 prospective and16 retrospective cases of GBS, which showed more than 60% to have cardiovascular abnormalities.In the present study , the evidence of autonomic dysfunction occurred in 6/7patients with AIDP and one patient with AMAN (87.5%). The higher incidence of dysautonomia in our patients'could be due to the predominantly AIDP subtype, longitudinal study starting as early as the first two days and longitudinal studies including, continuous recording of HR and BP, multiple cardiovascular autonomic function test in each patient upto 4th weeks of illness .The mean Hughes disability score and duration of illness at the time of presentation was 3.75 and 3.75$\pm$ 2.05 days respectively. The study was designed to include autonomic symptoms and quantitative measures of autonomic dysfunction and tried to devise a Normalized Total Autonomic Score with the intention to classify the degree of Autonomic dysfunction- severe, moderate and mild grades. The intention was to compare the type, spectrum and severity of autonomic dysfunction in the different stages of disease, week of illness and wanted to correlate the severity of dysfunction with the functional grade of disease and outcome, which has not been done earlier..Flachenecker et al[2] studied longitudinally cardiovascular autonomic function test upto 1 year of illness in 13 GBS and established 1st time Composite autonomic score to classify degree of autonomic dysfunction in different stages of illness. .Flachenecker did not include symptoms of autonomic dysfunction ,clinical cardiovascular manifestation of dysautonomia and SSR abnormalities in his scoring system. Flachenecker et al maximum composite score was 10 and composite score of >7 was considered as sevre autonomic failure..Twenty five percent of our patients had NTAS >16,which was arbitrarily chosen to be having severe autonomic dysfunction. Symptoms of dysautonomia were reported in 6/8 (75%)patients and the autonomic symptoms had started 1-5 days before the onset of motor weakness in three patients. Postural dizziness was reported in two patients'(25 %), in one patient postural dizziness preceded the onset of motor weakness by 5

days and this and persisted upto 10 weeks after the onset of neuropathy, inspite of improving motor weakness.The incidence of postural dizziness was comparable to the study by Singh (20.8%)[68]The bowel dysfunction was observed in 4/8 patients, 3 had evidence of constipation, where as one had both constipation and urinary retention.One patient had history of constipation 3 days preceding the motor weakness where as in another patient, urinary hesitancy started a day prior to the onset of motor weakness.The occurrence of constipation in our study group (50%), was higher than 14 % seen in the MGH series, where-as incidence of urinary retention (12.5 %) was comparable to the study by Ravn[22] 14/127 (11%) patients', but less than 30 % of Litchtnfelds series and 27% of MGH series[59].Anhidrosis,the direct evidence of impaired sympathetic output was observed in three patient (37.5%) which was less than Tuck and McLeod series[7] who reported anhidrosis in 6/7 of AIDP patients' studied . Only one patient had palpitation, which was much less than 29.17% reported by the study by Singh .[68]

The most frequent manifestation of autonomic dysfunction seen in our patients' was sinus tachycardia, which was similar to earlier reports.[2,7,68,69]and is believed to be due to sympathetic hyperactivity and/or parasympathetic underactivity. The sinus tachycardia was observed 6/ 8 patients' (75%) with GBS, which included one patient with AMAN in. The incidence of sinus tachycardia in this study which was less than that reported by Tuck and Macleod (100%),but was higher than 46% reported by Bansal and 37% of the MGH series.In 37.5% patients', a transient form of bradycardia was observed in this study, which was comparable to the study by Singh (33%), and is believed to be due to Parasympathetic overactivity or afferent baro receptor failure.In the present study, the bradycardia was episodic, spontaneous and usually preceded by highly labile BP and HR.None of our patient required atropine or needed trans-venous pacing of the heart,. as reported earlier in 7-34 % of patients [64,65]. Systemic hypertension, a sign of sympathetic overactivity or baroreceptor

failure was detected in 6/8 (75%) patients'and was persistent in 5 patients' and paroxysmal in one patient. The occurrence of hypertension in our patients was higher than 60% of Litchtnfelds series[59] and 27 % of Tuck and Macleod series.[7]Paroxysmal hypertension(3%) in Trux series [62] was correlated with quadriplegia and ventilatory dependence,which was not seen in our patients'.The maximum systolic and diastolic BP recorded in our patient was 200 mm Hg and 152 mmHg respectively .Hypertension and tachycardia were not treated pharmacologically, except in one patient as most episodes of severe hypertension were transient , and none had developed hypertensive crisis as reported earlier[7,56]and treatment was withheld due to the risk of incipient hypotension and bradycardia by beta blocker and antihypertensive agents'. One patient with persistent Hypertension was treated with low dose of Atenolol and there were no inadvertent side effects.Episodes of hypotension was detected in 4/8 patients' (50%)only during PE and was postural in one patient, where as in other three patients, this occured both spontaneously and during PE.The dysregulation of the parasympathetic and sympathetic systems' is responsible for alterations in vasomotor tone and peripheral vascular resistance, most often causing transient or in some cases persistent hypotension. The minimum BP recorded in our patient was 54/40 mm of Hg(systolic/diastolic BP) and all episodes of hypotension was treated with IV fluid challenge, and none of them required inotropic support's/8 patients' started having episodes of hypotension in this study, which was comparable to 42.8% of Tuck and Macleod series,[7]but was much less than 75% seen in the series of Pfeiffer et al.[64] Labile BP and HR was also very common form of clinical sign of autonomic dysfunction in this study and was observed in 75 % of the patients' at different points' of time, during the study period .Labile BP can be attributed to disturbances in the baroreceptor reflex pathway as well as changes in the catecholamine levels. [83] Labile HR(>30bpm), Labile BP(>40mmHg systolic BP) and bradycardia was reported as a predictor of significant arrhythmias, including risk factor for

asystole in a study by Winer .[84].Significant fluctuation of HR and BP, mainly episodes of tachycardia and hypotension was observed in 50% cases during plasma exchanges and was managed with frequent termination of procedure and IV fluid challenge. In one patient (pt number 3), there were frequent episodes of hypotension (upto 60/44 mm Hg) during PE,so, PE was discontinued and IV Ig was started, which she tolerated and had good outcome. In our patients', the number of of studies using non-invasive cardiovascular autonomic function tests were small due to the presence of motor deficits, facial and bulbar paresis, or use of mechanical ventilation mainly during the time of maximal weakness. HR response to deep breathing (I-E differences) was abnormal in 3/6 (50%) patients', whereas HR response to active standing (30:15 ratio)was abnormal in 1/2 patients', who were able to perform the test . Out of the two patients who were able to perform valsalva maneuver ,one had shown abnormal valsalva ratio(50%). 62.5% of patients' failed to have a rise of diastolic BP significantly in Cold immersion test, where as 50 % of the patients', who were able to stand unsupported, was showing significant fall of systolic BP on standing at or before 3 min.(>30mmHg).SSR was done in all eight patients, of which five had absent response (62.5%) (4 AIDP/ 1 AMAN) in both upper and lower limbs.All patients with absent SSR had evidence of dysautonomia. Three patients', in whom SSR was present, 2 had a mild degree of dysautonomia and the third patient did not develop autonomic dysfunction during the study period of three weeks'. The SSR abnormalities of our patients(5/8) was higher than 5/ 13 as reported by Taly et al,[76] but less than 12/12 in the series of Deniz Yerdelen.[77].SSR abnormalities in our patients did not correlate with the presence or severity of autonomic dysfunction significantly as reported by the earlier two studies[76,,77]The most common ECG pattern was sinus tachycardia as reported in earlier studies, but in one patient ECG showed T wave inversion in inferior and lateral leads, associated with ST segment depression in lateral leads, where as another patient showed T

wave inversion in anterior and lateral leads.Echocardiography and cardiac enzymes were found to be normal, and on further evaluation of both these patients with ST-T changes, this was considered probably related to activation of sympathetic nervous system leading to catecholamine associated mild myocardial injury.None of our our patients'showed any life threatening cardiac arrhythmias, unlike other published studies [85,86],probably this could be due to small number of patients' in our study.The normalized total autonomic score was maximum during progressive stage of the illness and subsequently started normalizing in the plateau phase. This was in accordance with the observation that clinically overt signs of autonomic dysfunction were mainly encountered during the early stages of the disease.[2,68,69] Resting tachycardia,bradycardia, episodes of hypertension and spontaneous hypotension started improving earlier than significant diurnal variation of HR and BP and bed side cardiovascular autonomic function tests'.Two of our patients were showing persistence of autonomic dysfunction inspite of improvement in the Hughes functional grade at 4th week of illness ,dysautonomia improved in one patient with persistence of ventilatory dependency at the termination of study(end of 4 weeks), where as in remaining five patients, dysautonomia was started normalizing with improving motor deficits. The degree of dysautonomia in our patients was variable and involving both sympathetic and parasympathetic components' of autonomic nervous system with considerable overlap. The evidence of sympathetic and/or parasympathetic over and /or under activity was present even in same patient at the same time or different points' of time, which was reported in an earlier studies.

It was difficult to locate the exact site of lesion in the present study. Two of our patients' had evidence of predominantly sympathetic dysfunction,one predominantly parasympathetic dysfunction where- as, the other four had evidence of both sympathetic and parasympathetic dysfunction of variable severity at different points in time.One patient(pt number 2) was showing significant postural dizziness, which was started 5 days prior to onset of motor

weakness and persisted upto 10 weeks even after significant improvement of Hughes functional grade, and she had postural fall of systolic BP >30 mm Hg and failure to rise of normal diastolic pressure in cold immersion test till the termination of study at the end of 3rd weeks with normal rise of HR during deep breathing and standing ,normal HR response in Valsalva test and absence of episodes of hypertension ,tachyacardia bradycardia or labile BP and HR during the entire study period and suggested probable involvement of efferent sympathetic fibers predominantly with intact baro receptor functions .But,the SSR was normal.One patient was showing persistent sinus tachycardia ,abnormal rise of diastolic BP in cold immersion test, significant postural fall of systolic BP, normal rise of HR following deep breathing and standing and suggested combined involvement of afferent baroreceptor and Sympathetic efferent with absence of SSR in both upper and lower limbs and significant bulbar dysfunction.One of our patient was showing significant hypertension and sinus tachycardia, labile HR and BP ,upto 4th weeks of illness ,failure to rise of HR on deep breathing and standing with presence of SSR in both upper and lower limbs and suggested abnormal baroreceptor function .This patient was not showing clinically evident bulbar dysfunction.Our patient who had the maximum normalized autonomic score (NTAS) 19.2 was showing maximum fluctuation of systolic BP over 24 hrs(mean daily fluctuation of systolic BP 81.66 mmHg), intolerance to PE and ST changes suggestive of myocardial injury. Labile systolic BP (>40 mmHg/day) was the most important predictor of life threatening arrhythmias in an earlier study.[83] The NTAS was not showing any correlation with symptoms of orthostatic intolerance, as patient who was having significant postural dizziness was grouped in the mild autonomic failure category in present study with maximum NTAS 8.35 during the progressive stage of disease. The only patient who had AMAN, was found to have a moderate degree of dysautonomia, including sympathetic,Parasympathetic,Sudomotor and bowel dysfunction which started normalizing by the 2nd week and improved by the end of

3rd weeks with non improving motor disability. The pattern of involvement of autonomic nervous system in AMAN of our study was different from Asahina's series of patients, who studied 8 AMAN and compared them with 7 AIDP cases[3].According to Asahina's study, AIDP have mainly cardiovascular sympathetic hyperactivity with sudomotor hyper or hypofunction but AMAN had mainly sudomotor hypofunction with preserved cardiovascular function.This differences probably may be due to the fact that Asahina's patients' had milder grade of disease. There was one patient in this study in whom dysautonomia was not observed, and this patient had AIDP, with a hyper acute onset of illness , presence of bifacial and bulbar involvement with Hughes functional grade of 4 at the peak of illness .The present study was not showing any significant correlation between presence or severity of dysautonomia(NTAS) with grade of motor weakness (p=0.537) or sensory disturbances(p=0.64), although most studies showed correlation [2,62], but a few other studies had shown no correlation [59,68,69]. In contrast to other studies[2] our study was not showing correlation of severity of dysautonomia with respiratory compromise requiring mechanical ventilation .The severity of dysautonomia was showing positive correlation with older age of onset of illness, which was statistically significant.(P=0.03)

Limitations of study

1) Small sample size.
2) All cardiovascular autonomic function test were not be performed in every patient mainly at the peak of motor weakness

CONCLUSIONS

1) The present study demonstrated high incidence of autonomic dysfunction in patient With GBS (87.5%).

2) Autonomic dysfunction was detected in 6/7 patients' with and one patient with AMAN. Fifty percent patients had evidence of both sympathetic and parasympathetic dysfunction, 25%had predominantly sympathetic dysfunction,where as 12.5% patients had predominantly parasympathetic dysfunction

3) The degree of dysautonomia (NTAS) was maximum during the first 2 weeks of illness in majority of patients' and started normalizing thereafter.

4) Severe Dysautonomia was seen in 25 % patients', moderate degree of dysautonoma in 37.5 % patients,mild degree in 25 % patients

5) The severity of dysautonomia correlated with older age (>45 yrs) of onset of illness, which was statistically significant

6) The presence and severity of dysautonomia(NTAS) did not show correlation with motor disability,sensory disturbances and use of mechanical ventilation

7) The autonomic dysfunction was not fatal in this study

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Appendix 1

DATA COLLECTION PROFORMA

Name:	**Address:**
Hospital Number:	**Telephone/E-mail:**
Dob: **Age:**	**Seen by:**

History Date of diagnosis ::

History Days since onset of symptoms:: 1 week ( ) 2 weeks ( )

3 weeks( ) 4 weeks ( )

Preceding history :- Diarrhoea ( ) URI ( ) Vaccination ( )

Code – diarrhoea –yes – 1 , URI – yes -2 , Vaccinat – yes – 3

Co-morbidities :

Hypertension Y / N Smoking Y / N

Diabetes mellitus Y / N

Chronic diarhea Y/ N Renal failure Y / N

Coding for Symptoms

Sensory Parasthesia	1 .Symptoms limited to fingers or toes	2 .Symptoms extend to ankle or wrist	3. Symptoms extend to knee or elbow	4. Symptoms above knees or elbows, or functionally disabling	5 Facial involvement	6 Trunkal involvement
Sensory loss	1 Symptoms limited to fingers or toes	2 Symptoms extend to ankle or wrist	3 Symptoms extend to knee or elbow	4 Symptoms above knees or elbows, or functionally disabling	5 Facial involvement	6 Trunkal involvement
pain	1 .Symptoms limited to fingers or toes	2 .Symptoms extend to ankle or wrist	3. Symptoms extend to knee or elbow	4. Symptoms above knees or elbows, or functionally disabling	5 Facial involvement	6 Trunkal involvement
Type of pain	1 Burning type	2 Pricking type				
Motor	1 Difficulty in hand grip	2 Difficulty in combing, reaching up to shelf	3 Difficulty in turning in bed	4 Bulbar symptoms		
	5 Difficulty in gripping foot wear, footwear slipping off with knowledge	6 Twisting of ankle, buckling of knee	7 Difficulty in getting up from squat	8 Complete paralysis		

Cranial nerve involvement

Cranial nerve	**Day 1**	**Day 2**	**Day 3**	**Day 7**	**2nd week**	**3rd week**	**4th weeks**
Fundus							
Pupil							
Eye movement							
Trigeminal							
Facial							
Vest cochlear							
Palate							
Sternomastoid							
Tongue							

Motor Examinations

Bulk and Tone

	week 1	week 2	week 3	week 4
Wasting				
Tone				

0 = normal, 1 = decreased , 3 increased

Power

	week 1		week 2		weeek 3		week4	
Power	R	L	R	L	R	L	R	L
Neck flx								
Neck ext								
Trunk								
Should Ab								
Should Add								
Elbow Flx								
Elbow Ext								
Wrist Flx								
Wrist Ext								
Hip Flx								
Hip Ext								
Knee Flex								
Knee Ext								
Dorsiflx								
Plantar								

MRC Grading

0 No movement

1 Flicker

2 Movement not against gravity

3 Movement against gravity

4 Against gravity

l 5 Normal

	week 1		week 2		week 3		week 4	
Reflexes	R	L	R	L	R	L	R	L
Biceps								
Brachiorad								
Triceps								
Knee								
Ankle								
Sup abd								
plantar								

Reflex Grading

0 Absent

+/- Present with reinforcement

\+ Decreased

++ Normal

+++ Increased

C With clonus

Symptoms of dysautonomia

Day 1	Day 2	Day 3	Day 7	2nd week	3rd week	4th weeks

Clinical cardiovascular function

Day 1	Day 2	Day 3	Day 7	2nd week	3rd week	4th weeks
Resting HR						
Fluctuation of HR						
Systolic BP						
Diastolic BP						
Fluctuation of SBP						

Clinical autonomic function test

Day 1	Day 2	Day 3	Day 7	2nd week	3rd week	4th weeks
I-E differences						
30:15 ratio						
Valsalva ratio						
Postural fall of SBP						
Cold immersion test						

Bowel dysfunction	**Day 1**	Day 2	**Day 3**	**Day 7**	**2nd week**	**3rd week**	**4th weeks**
Nil							
Bloating							
Sluggish bowel sound							
Constipation							
Hyperactive bowel sound							

Bladdar dysfunction

Bladdar dysfunction	**Day 1**	**Day 2**	**Day 3**	**Day 7**	**2nd week**	**3rd week**	**4th weeks**
Nil							
Frequency							
Urgency							
Hesitancy							
Retention							

Sweating abnormality

Sweating abnormality	Day 1	Day 2	Day 3	Day 7	2nd week	3rd week	4th weeks
Nil							
Cold to touch							
Hot to touch							
Anhidrosis							
Hyperhidrosis							
Episodic flushing							
Episodic sweating							

a-localised to feet/LL

b-localised to hand /UL

c-localised to trunk

d-localised to face

e -Generalised

Electrophysiology

	week1	week2	week3	week4
NCV				
EMG				
SSR				

0 = normal, 1 = abnormal

Type of Neuropathy : AIDP /AMSAN/ AMAN /MF

CSF – TC ECG Changes

DC

SUGAR

PROTEIN

Treatment received

Plasmapheresis Days of illness amount remark

IV Ig

Appendix 2 **Informed Consent**

PATIENT'S INFORMATION

I understand that department of Neurological sciences is doing a study to:

1.To study autonomic nervous system involvement in patient with Guillain- Barré Syndrome (GBS)

2.To assess the clinical significance of the autonomic nervous system involvement in such patients

3.To assess the relation of autonomic dysfunction with clinical severity of GBS .

The study involves collection of patient information, clinical data and test reports done as part of regular clinical care. I also understand that some of the tests done in connection with the study may directly benefit me whereas the other tests are likely to benefit other patients with the disease.

I understand that my withdrawal from the study, at any time will not affect the treatment being given.

Study Title: **Study of autonomic dysfunction in patients with Guillain-Barré Syndrome (GBS)**

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age:_____

Please initial box

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission

to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

Appendix 3 Master chart

Chart showing clinical characteristics of patients

Patient Number	1	2	3	4	5	6	7	8
Age(yrs)	19	22	47	60	44	19	30	43
Sex	M	F	F	F	M	M	M	M
Spectrum of GBS	AIDP	AIDP	AIDP	AIDP	AMAN	AIDP	AIDP	AIDP
Days of illness at presentation	2	2	4	2	3	4	8	5
DS at admission	5	2	4	4	4	4	3	4
DS at discharge/termination of study	3	2	3	3	5	3	3	3
Onset to nadir (days)	12	10	12	2	7	1	20	11
Antecedent events	Nil	Myalgia & arthralgia	Myalgia & arthralgia	Nil	Diarrhoea	Diarrhoea	Nil	URTI
Cranial nerve involvement	Bifacial& bulbar	Nil	Nil	Bifacial	Bifacial & Bulbar	Bifacial & Bulbar	Bifacial	Bifacial& Bulbar
Sensory symptoms/sign	Nil	Yes	Yes	Yes	Yes	Nil	Yes	Yes
Bladder dysfunction	Nil	Nil	Nil	Yes	Nil	Nil	Nil	Nil
Bowel dysfunction	Nil	Nil	Nil	Yes	Yes	Nil	Nil	Yes
Sweating abnormalities	1	Nil	Yes	Yes	Nil	Nil	Nil	Nil
SSR Abnormalities	Yes	Nil	Yes	Yes	Yes	Nil	Nil	YES
ECG changes	Nil	Nil	Yes	Yes	Nil	Nil	Nil	Nil

Chart showing clinical cardiovascular function upto 4th week of illness

Patients Number		1	2	3	4	5	6	7	8
Resting HR (bpm)	Day 1	122	78	110	104	114	92	NA	116
	Day2	130	104	114	114	110	100	118	112
	Day3	116	110	122	120	112	98	120	112
	Week2	114	90	130	116	98	78	114	136
	Week3	110	74	96	106	102	82	108	92
	Week4	86	NA	92	NA	76	NA	110	NA
Daily Fluctuation of HR (Mean)	Day 1	80	20	68	52	56	24	NA	50
	Day2	90	30	62	49	62	30	36	56
	Day3	65	28	57	60	50	22	46	48
	Week2	65	24	54	62	40	18	70	80
	Week3	54	20	40	38	44	14	24	34
	Week4	60	NA	18	NA	22	NA	29	NA
Systolic BP (mm of Hg)	Day 1	150	90	188	176	168	126	NA	156
	Day2	152	100	152	160	170	118	162	160
	Day3	148	104	154	130	158	120	160	166
	Week2	164	108	152	134	152	118	146	132
	Week3	166	102	160	128	120	110	148	110
	Week4	122	NA	140	NA	130	NA	134	NA

Chart showing clinical cardiovascular function upto 4th week of illness

Patients Number		1	2	3	4	5	6	7	8
Diastolic BP (mm of Hg)	Day 1	92	50	114	104	134	70	NA	108
	Day2	86	62	100	94	98	78	134	102
	Day3	94	60	110	74	80	88	98	92
	Week2	96	70	136	80	100	74	90	86
	Week3	80	78	88	78	68	70	92	72
	Week4	70	NA	72	NA	72	NA	94	NA
Daily Fluctuation of Systolic BP (Mean)	Day 1	78	20	146	80	86	22	NA	50
	Day2	7	22	70	30	100	30	101	64
	Day3	52	22	78	38	84	34	64	58
	Week2	72	26	49	32	60	18	58	50
	Week3	70	14	78	36	22	34	50	20
	Week4	38	NA	60	NA	24	NA	20	NA

Chart showing cardiovascular autonomic function test upto 4th week of illness

Patients Number		1	2	3	4	5	6	7	8
30:15 ratio	Day 1	ND	1.02	ND	ND	ND	ND	ND	ND
	Day2	ND	1.6	ND	ND	ND	ND	ND	ND
	Day3	ND	2	ND	ND	ND	ND	ND	ND
	Week2	ND	1.03	ND	ND	ND	1.8	0.09	ND
	Week3	ND	1.08	ND	ND	ND	1.06	0.08	1.08
	Week4	ND	NA	ND	NA	ND	NA	1.03	NA
I-E differences	Day 1	ND	18	8	10	ND	18	NA	ND
	Day2	ND	20	10	12	ND	16	NA	ND
	Day3	ND	18	8	16	ND	19	NA	ND
	Week2	ND	19	12	12	ND	18	12	20
	Week3	ND	16	10	10	ND	20	10	18
	Week4	ND	NA	10	NA	ND	NA	10	NA
Valsalva ratio	Day 1	ND	1.42	0.8	ND	ND	ND	NA	ND
	Day2	ND	1.64	0.6	ND	ND	ND	ND	ND
	Day3	ND	1.44	0.9	ND	ND	ND	ND	ND
	Week2	ND	1.82	1.01	ND	ND	ND	ND	ND
	Week3	ND	1.76	1.14	ND	ND	ND	ND	ND
	Week 4	ND	NA	1.18	NA	ND	NA	ND	NA

Chart showing cardiovascular autonomic function test upto 4th week of illness

Patients Number		1	2	3	4	5	6	7	8
Fall of SBP on standing upto 3 min. (mm of Hg)	Day 1	ND	34	ND	ND	ND	8	NA	ND
	Day2	ND	38	ND	ND	ND	6	ND	ND
	Day3	ND	40	ND	ND	ND	10	ND	ND
	Week2	ND	34	ND	ND	ND	8	ND	ND
	Week3	ND	36	ND	ND	ND	4	+6	14
	Week4	ND	NA	ND	NA	ND	NA	-8	NA
Cold immersion test (mmHg)	Day 1	8	6	2	12	16	18	NA	20
	Day2	10	4	8	13	18	16	NA	22
	Day3	14	8	6	16	18	20	NA	18
	Week2	6	6	2	13	20	16	16	14
	Week3	12	8	2	12	16	18	18	12
	Week4	18	NA	12	NA	22	NA	16	NA