IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 4 Ser. 14 (April. 2019), PP 01-07
www.iosrjournals.org

Autonomic Function Testing and Ganglioside Antibody Testing In Correlation with Short Term Outcome in Guillain – Barre Syndrome

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Abstract:
Introduction: *Guillain–Barré syndrome, which is characterized by acute are flexic paralysis with albuminocytologic dissociationis currently the most frequent cause of acuteflaccid paralysis worldwide and constitutes one of the serious emergencies inneurology.Autonomic dysfunction (AD) is a common and important complication in Guillain-Barré syndrome and may be the cause of significant morbidity or death.We conducted the present study with an aim to include antibody testing and autonomic function testing in GBS patients and see if they carried any clinical significance.*
Aims and Objectives of the Study: *1. To study association between antiganglioside antibodies and outcome inGuillain-Barre Syndrome.2. To study autonomic involvement and antiganglioside antibodies in different subtypes of Guillain-Barre Syndrome.*
Methods: *A sample of 50 subjects fulfilling the inclusion and exclusion criteria were taken and different types of Guillain Barre Syndrome were analysed. Autonomic functioning and Anti-ganglioside antibodies were obtained and their association was assessed.*
Results: *Autonomic dysfunction was seen in 34(68%) patients.IgG antibodies are positive in only 14% of the cases and 44% of AMAN patients.There was no relation between the antiganglioside antibodies and outcome of GBS.*
Conclusions: *Antiganglioside antibodies showed significant association with axonal variants but they didn't show any correlation with their outcome.GT1b antibody was the commonest antiganglioside antibody associated with the axonal variant.*
Key words: *Guillain Barre Syndrome, Autonomic dysfunction, Antiganglioside antibodies*

Date of Submission: 04-04-2019 Date of acceptance: 19-04-2019

I. Introduction

Guillain–Barré syndrome, which is characterized by acute areflexic paralysiswith albuminocytologic dissociation (i.e., high levels of protein in the cerebrospinalfluid and normal cell counts), was described in France in1916[1]. Since poliomyelitishas nearly been eliminated, the GBS is currently the most frequent cause of acuteflaccid paralysis worldwide and constitutes one of the serious emergencies inneurology.

Various studies of the immunopathogenesis of the GBS suggest that the disease actually encompasses a group of peripheral-nerve disorders, each distinguished by the distribution of weakness in the limbs or cranial-nerve–innervated muscles and underlying pathophysiology. There is substantial evidence to support an autoimmune cause of this syndrome, and the autoantibody profile has been helpful in confirming the clinical and electrophysiological relationship of the typical GBS to certain other peripheral-nerve conditions[2-4].

Autonomic dysfunction (AD) is a common and important complication inGuillain-Barrésyndrome and may be the cause of significant morbidity or death.About 20% of all GBSpatients have symptoms involving both sympathetic andparasympathetic fibers. This rate rises to 75% in patients with quadriplegia[5].

The study of distribution of GBS subtypes in our patientpopulation was doneby S.Gopi et al in 2003-2006 ,which showed that axonal variants weresignificantlymore common than AIDP. In that study antiganglioside antibodies andautonomicfunction testing were not studied. We conducted the present study with an aim toinclude antibody testing and autonomic function testing in GBS patients and see ifthey carried any clinical significance.

Aims and Objectives of the Study: 1. To study association between antiganglioside antibodiesand outcome inGuillain-Barre Syndrome.
2. To study autonomic involvement and antiganglioside antibodies in differentsubtypes of Guillain-Barre Syndrome.

II. Materials and Methods

Study Design: Prospective observational study
Subjects: We studied 50 consecutive patients aged above 12 years with clinicaldiagnosis of GBS admitted in the departments of Neurology and General Medicine atKing George Hospital, Visakhapatnam who fulfilled the clinical criteria of GBS(Ashburys diagnostic criteria[6]).

The demographic data recorded included age, sex, duration of illness andpreceding antecedent illness. Detailed clinical history and neurological examinationwere performed.The study period was 2years. Subjects wererecruited into the study after informed consent.

Inclusion Criteria:

- All patients admitted with clinical diagnosis of GBS were included in the study and divided into different subtypes based on criteria.
- Patients aged above 12 years were included.

Exclusion Criteria:

- Arrhythmia
- Ischemic or other heart diseases
- Chronic obstructive airway disease
- Diabetes mellitus
- Hypothyroidism
- CNS disease that may affect autonomic nervous system
- Drugs affecting autonomic nervous system.

Functional disability*:* Patient disability at the peak of the deficit was assessed usingModified Hughes functional grading scale[7], MRC sum score and also assessed atthe end of 3 months.

MRC Sum score is calculated at the time of admission and at the end of 3months.**Sum of Medical Research Council scores of six muscle groups,**including shoulder abductors, elbow flexors, wrist extensors, hip flexors, kneeextensors, and foot dorsiflexors on both sides, ranging from 60 (normal) to 0(quadriplegic). The MRC score of an individual muscle group ranges from 0 to 5.

Nerve conduction studies were performed within 4 weeks of onset ofneurological symptoms and were repeated if the initial conduction studies werenormal. Motor conduction studies were performed on median, ulnar, tibial andperoneal nerves using conventional techniques. Sensory nerve conduction studieswere performed on median, ulnar and sural nerves using conventional techniques.

Patients were classified as having AMAN or AIDP on the basis of theelectrodiagnostic criteria proposed by **Ho et al[8].** A diagnosis of acute sensory axonal neuropathy (ASAN) was made whenmotor conduction studies were normal but sensory nerve conduction studies showeddecreased or absence of sensory nerve action potentials of sural nerves.

Antiganglioside antibodies:

The serum antiganglioside antibodies (IgG) were assayed using Euroimmune(Germany) kits. The EUROLINE test kit provides a qualitative in vitro assay forhuman antibodies of class IgG to the seven gangliosides GM1, GM2, GM3, GD1a,GD1b, GT1b and GQ1b in serum or plasma.

Clinical testing of autonomic neuropathy function:

Sympathetic functions are assessed by postural hypotension, sustainedhandgrip, parasympathetic functions assessed by resting heart rate, heart rateresponse to deep breathing, valsava ratio, heart rate response to standing by CANSmachine in all patients.

Sympathetic Skin Response:

For the palmar SSR, surface electrodes were used with the active recordingelectrode placed on the palm of the hand and the reference electrode located at thewrist on the dorsum of the hand. SSR parameter included the latency to the onset ofdepolarization which was indicated by the first continuous deflection from thebaseline.

Statistical Analysis:

The data was presented as mean ± standard deviation or percentage ofcohort affected. The significance between means of two parameters was comparedusing unpaired 't' test. The p value of less than 0.05 was considered statisticallysignificant. For the statistical analysis SPSS software was used.

III. Results

The study included 50 consecutive cases with clinical diagnosis of GBS admitted in the Department of Neurology and General Medicine, King George Hospital, Visakhapatnam. The basic characteristics of the cases is given in the below table. There were 33 (66%) male and 17 (34%) female patients (M:F = 1.94:1). The mean age was 36.24±13 years (range 14 to 65 years). 15 (30%) patients had antecedent illness.

	Number (n)	Percentage
Male	33	66
Female	17	34
Mean age±SD	36.24 ± 13	
Motor weakness	45	90
Sensory symptoms	33	66
Cranial nerve involvement	23	46
Respiratory muscle weakness	10	20
Autonomic Symptoms	16	32
Antecedent Illness	15	30
CSF Albuminocytologic dissociation	27	54

Table1: Demographic and clinical features of GBS patients

GBS Subtypes:In this study, AIDP accounted for 34% of GBS cases, 62% were constituted by axonal variants (AMAN,AMSAN,ASAN), 4% by MFS variant. Both AIDP and axonal variants had male preponderance.

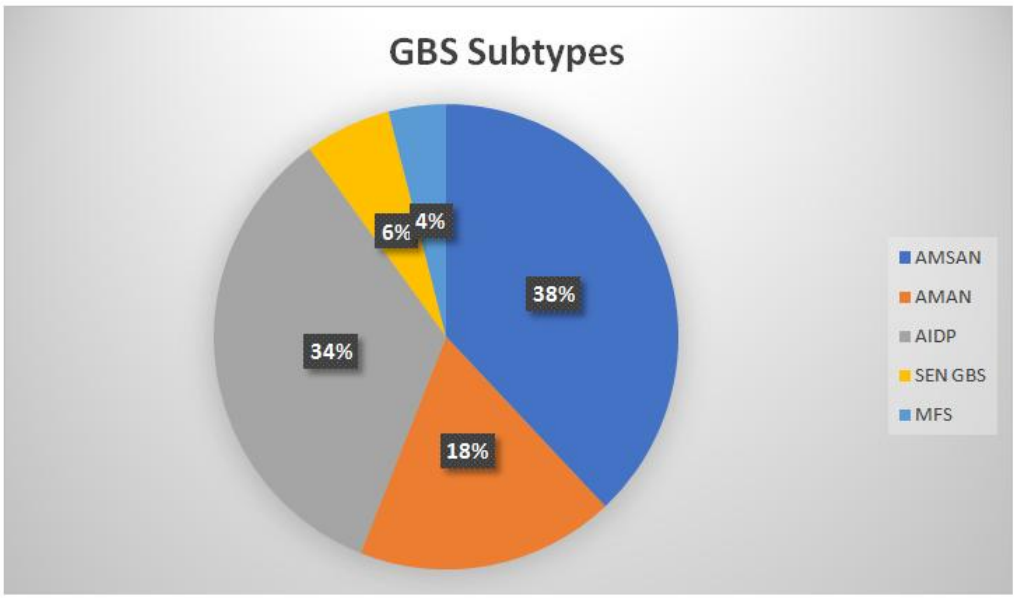

Figure 1: Distribution of GBS subtypes

Autonomic dysfunction: Autonomic dysfunction was seen in 34(68%) patients. Sympathetic dysfunction was seenin 32(64%) patients. Parasympathetic involvement was seen in11(22%). In 9 patients both sympathetic and parasympathetic involvement was seen.Sympathetic skin response (SSR) is not recordable in 13(26%) patients.

There was not much difference in sympathetic dysfunction in axonal and demyelinating GBS(45% vs 52%). Both sympathetic and parasympathetic dysfunction were present in 19% of axonal GBS compared to 17% of demyelinating GBS. Parasympathetic dysfunction was present only in Axonal GBS(6%).
Sympathetic Skin Response (SSR) was not recordable in 25% of axonal GBS and 29% of demyelinating GBS.

Antiganglioside antibodies:

IgG antibodies are positive in only 14% of the cases and 44% of AMAN patients. The commonest IgG antibodies seen in our study were GT1b in 4(57%) patients, followed by GQ1b in 2 (28%) patients. One out of 2 MFS cases had GQ1b antibody positive.

GBS Subtype	Number	Antibody positive	Percentage	p value
AIDP	17	0	0	
AMAN	9	4	44%	
AMSAN	19	2	10%	0.01
ASAN	3	0	0	
MFS	2	1	50%	

Table 2: Antibodies in various GBS subtype

Functional disability: Most of the patients with AIDP presented with Hughes functional disability grade of 2 or 3 whereas axonal forms presented with Hughes functional disability grade of 3 or 4. 41 patients recovered completely with Hughes functional disability grade of 1 at the end of 3 months. Of the remaining 8 cases,5cases of AMAN and 3 cases of AMSAN had incomplete recovery with Hughes grade of 2 or 3.
MRC Sumscore and Erasmus GBS Outcome score were calculated at the time of admission. Patients with axonal GBS were found to have lower MRC Sum score compared to AIDP.

Management: Patients with Modified Hughes functional grade 2,3 are treatedconservatively with steroids whereas with grades 4,5 are treated with IVIg. One patient needed mechanical ventilator.
The mean of MRC sum score at nadir in patients with autonomic dysfunction (40.76±15.871) was found to be significant compared to patients without autonomic dysfunction (49.38 ± 9.025) (p value=0.05). The rest of the outcome parameters were not significant.

	Antibodies	N	Mean	Std. Deviation	p value
HUGHES at nadir	Present	7	2.86	1.069	
	Absent	43	2.74	.928	.771
HUGHES at 3 months	Present	7	1.57	.787	.152
	Absent	43	1.19	.627	
Erasmus outcome score	Present	7	3.143	1.1802	.686
	Absent	43	2.965	1.0544	
MRCscore at nadir	Present	7	35.71	21.554	.127
	Absent	43	44.79	12.963	
MRCscore at 3 months.	Present	7	48.86	17.958	.282
	Absent	43	54.37	11.441	

Table 3: Outcome vs Antiganglioside antibodies

Outcome of GBS is measured by calculating Hughes grade, MRC sum score at the end of 3 months, Erasmus outcome score at nadir. There was no relation between the antiganglioside antibodies and outcome of GBS.The mean score of Hughes grade at 3 months in axonal GBS (1.39 ± 0.803) was found to be significant when compared to demyelinating GBS (1.0) (p value=0.05).The mean MRC sum score at 3 months in axonal GBS (50.52 ± 14.957) was found to be significant when compared to demyelinating GBS (58.47 ± 2.787) (p value=0.03).

IV. Discussion

Age: GBS affects all ages, but is more frequent in adults over 40 years of age.Mean age in our study was 36 years, similar to the previous studies.

Sex: The classic form of GBS is a nonseasonal illness that affects persons of allages, but males are more often affected than females (1.5 : 1). In present study, there was male gender predominance (M:F = 1.94:1).

GBS Subtypes:

Study	Year	Region	Age	Criteria	Axonal GBS%
S.Gopi et al	2003-2006	India	All ages	Ho	55 of 110
Nagasawa et al	2006	Japan	1-15	Ho	48 of 31
Nachamkin et al	2007	Mexico	1-17	Hadden	48 of 95
Kushnir et al	2007	Israel	15-84	Hadden	37 of 40
Kalita et al	2008	India	All ages	Ho	14 of 51
Gupta et al	2008	India	All ages	Ho	11 of 142
Islam et al	2010	Bangladesh	All ages	Hadden	67 of 100
Uncini et al	2010	Italy	No information	Ho Hadden	18 of 55 18 of 55
Akbayram et al	2011	India	0-14	Ho	31 of 36
Sekiguchi et al	2012	Japan Italy	12-81 9-79	Ho&Hadden Ho&Hadden	23 of 103 17 of 53
Ye et al	2013	Notheastern China	3-75	Hadden Ho	33 of 99
Present study	2015	India	>12 yrs	Ho	62 of 50

Comparison of % of GBS subtypes between present study andother studies

Antiganglioside antibodies:

In the present study all 50 patients were tested for IgG antibodies. IgG antibodies are positive in only 15% of the cases and 44% of AMAN patients. The commonest IgG antibodies seen in our study were GT1b in 4(57%) patients, followed by GQ1b in 2 (28%) patients. One out of 2 MFS cases had GQ1b antibody positive (p value =0.01)

This result is almost similar to the following studies by Ho et al and Willison and Yuki et al. In AMAN, antibodies against GM1 and GD1a can be detected in about half of the patients (Ho et al., 1999)[9], whereas antibodies against GQ1b can be found in 80%–90% of patients with Miller Fisher syndrome (Willison and Yuki, 2002)[10].

In a Japanese study, however, only 12 (48%) of 25 patients with GBS and raised titres of antibodies against GM1 or GD1a were classified by the electrodiagnostic criteria as having AMAN.

In another study in adult patients with GBS from South India, of the 10 patients of AMAN, 8 patients had GD1b antibody in the serum (unpublished data)[11]. The significance of the GD1b antibody in GBS has been studied earlier. Nachamkin*et al*.[12] reported a higher proportion of children with AMAN having GD1b antibody from Mexico.

Outcome vs Antiganglioside antibodies:

In the present study, no correlation between the presence and absence of antibodies with the outcome was found.The presence of antiganglioside antibodies in serum was not found to be of much use in predicting the outcome. However, the absence of antibodies has been shown to be associated with poor outcome.

In a study done in NIIMHANS, the study aimed to detect antiganglioside antibodies in the sera of patients with Gullain Barre syndrome and correlate their presence with clinical features, electrophysiological studies and outcome. 20 patients with GBS were evaluated clinically and electrophysiologically. Serological assays for antibodies against GM1, GD1a and GD1b gangliosides were carried out by ELISA. 12 patients tested positive, who had antibodies against all three gangliosides, one against both GM1 and GD1a, one against GM1 and GD1b while antibodies against GM1, GD1a or GD1b alone were seen in two, five and one patient respectively. No significant correlation was noted between the presence or type of antibody clinical features, electrophysiological findings and outcome.

The incidence of antiganglioside antibodies in the population of patients described was 18 % for GM1 and 24% for GD1a although not powered to detect small statistical differences, no consistent distinction was seen in the severity of involvement among the patients who had the antibody. The presence of anti ganglioside antibodies was not found to be of much use in predicting the outcome although it is observed that absence of anti ganglioside antibodies was associated with poor recovery. In agreement with the present study Vriesendrop et al[13]also observed that patients with anti ganglioside antibodies had relatively good recovery.

Outcome vs autonomic dysfunction: The mean of MRC sum score at nadir in patients with autonomic dysfunction (40.76 ± 15.871) was found to be significant compared to patients without autonomic dysfunction (49.38 ± 9.025) (p value=0.05). This result is comparable to the study by Flachenecker et al[14].

V. Conclusions

1. Antiganglioside antibodies showed significant association with axonal variants but they didn't show any correlation with their outcome.
2. GT1b antibody was the commonest antiganglioside antibody associated with the axonal variant.
3. In cases where clinical and electrophysiological studies are inconclusive, antibodies may be helpful in diagnosing axonal variants.
4. The patterns of autonomic involvement are qualitatively different between AIDP and AMAN.
5. Our results suggest that SSR and other autonomic tests may be used for early detection of any autonomic involvement in patients with GBS but they didn't show any correlation with outcome.

Limitations:

1. Small sample size and short term follow up.
2. Most of the cases are recruited from neurology OPD and patients had a functional disability,Hughes grade 2 or 3 which resulted in a good outcome.
3. Autonomic functions were modified in nonambulatory patients, so results cannot be standardised and compared.
4. Only IgG Antiganglioside antibodies were tested.

References

[1]. Guillain G, Barré JA, Strohl A. Sur un syndrome de radiculonévrite avec hyperalbuminose du liquidecéphalo-rachidien sans réactioncellulaire: remarques sur les caractèrescliniques et graphiques des reflexes tendineux. Bulletins et memoires de la Société des Médecins des Hôpitaux de Paris 1916;40:1462-70.
[2]. Sekiguchi Y, Uncini A, Yuki N, et al. Antiganglioside antibodies are associated with axonal Guillain-Barré syndrome: a Japanese-Italian collaborative study. J Neurol Neurosurg Psychiatry 2012;83: 23-8.
[3]. Ito M, Kuwabara S, Odaka M, et al. Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum: clinical analysis of 581 cases. J Neurol 2008;255:674-82.
[4]. Ito M, Matsuno K, Sakumoto Y, Hirata K, Yuki N. Ataxic Guillain-Barré syndrome and acute sensory ataxic neuropathy form a continuous spectrum. J Neurol Neurosurg Psychiatry 2011;82:294-9.
[5]. Asahina M, Kuwabara S, Suzuki A, Hattori T. Autonomic function indemyelinating and axonal subtypes of Guillain-Barré syndrome. Acta Neurol Scand2002;105:44-50.
[6]. Ashbury, A.K., Cornblath, D.R., 1990. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 27 Suppl, S21–S24.
[7]. Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial of Prednisolone in acute polyneuropathy. Lancet 1978;2:750-3.
[8]. Ho TW, Li CY, Ho TW, Xue P, Macko C, Gao CY, *et al*. GB syndrome in northern China: The spectrum of neuropathological changes in clinically defined cases. Brain 1995;118:577-95.
[9]. Ramos-Alvarez M, Bessudo L, Sabin AB (1969). Paralytic syndromes associated with noninflammatory cytoplasmic or nuclear neuronopathy. Acute paralytic disease in Mexican children, neuropathologically distinguishable from Landry-Guillain-Barre´ syndrome. JAMA 207:1481– 1492.
[10]. Willison HJ, O'Hanlon GM (1999). The immunopathogenesis of Miller Fisher syndrome. J Neuroimmunol 100:3–12.
[11]. Ashok Kumar Reddy B, Meena AK. Clinical, electrophysiological patterns and outcome of Guillain-Barré syndrome in relation to antiganglioside antibodies. *Dissertation*: NIMS, 2007.
[12]. Nachamkin I, ArzarteBarbois P, Ung H, Lobato C,Gonzalez Rivera A, Rodriguez P, et al. Patterns of Guillain–Barré Syndrome in children: results from a Mexico population. Neurology 2007;69:1665–1671.

[13]. Vriesendrop FJ, Mishu B, Blaser MJ, Koski CL. Serum antibodies to GM1, GDlb, peripheral nerve myelin and campylobacter jejuni in patients with GB syndrome and controls: Correlation and prognosis. Ann Neurol 1993;34:130-5.
[14]. Flachenecker P (2007). Autonomic dysfunction in Guillain- Barre´ syndrome and multiple sclerosis. J Neurol 254(Suppl. 2):II96–101.

Dr. A. Gopi Krishna. "Autonomic Function Testing and Ganglioside Antibody Testing In Correlation with Short Term Outcome in Guillain – Barre Syndrome." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 04, 2019, pp 01-07.