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A study of utility of delta IgG as a prognostic marker in Guillain Barre Syndrome after IV immunoglobulin treatment

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***Abstract*---**Background: Guillain-Barré syndrome (GBS) is an acute onset immune-mediated disease affecting the peripheral nerve also its root Plasma exchange(PE) and intravenous immuno globulin(IVIG) have given evidence for faster recovery in GBS(4). IVIG treatment is comparatively costly but hospital stay duration is reduced.Other options include corticosteroids but have not shown benefit. Mortality of GBS is around 3%. Around 20 % patients have persisting neurological deficits and one half of these have severe disability. After a standard dose of IVIg treatment, GBS patients show a large variation in pharmacokinetics of IgG, which may be related to clinical outcome. The therapeutic dose of IVIg for GBS was empirically set at 2g per kg body weight, based mainly on the clinical experience in patients with immune deficiencies. Not all patients of GBS, however, show a good recovery after this standard dose. IVIg clearance may depend on disease severity and vary between individuals, implying that this dose may be suboptimal for some patients who might need DOSE adjustments for others the standard dose might be sufficient. Aims and Objectives: To study and determine the serum DELTA IgG values and evaluate its utility in the prognosis of Guillain Barre Syndrome after IVIG treatment. Materials and Methods: The study was conducted in hospitals associated with KMC, Mangalore. Study Design: Prospective Analytical study. Study Population: All diagnosed cases of Guillain barre syndrome receiving standard IVIg treatment. Study Duration: September 2018 to August 2020. Results: Using Karl Pearson's correlation coefficient, Negative correlation exists between GBSD scores at 3 months to that of Delta IgG (difference in serum IgG levels at 14th day to that of the baseline) and it is to be statistically highly significant meaning higher the Delta IgG lesser is the GBSD

score at 3 months reflecting better clinical outcome with high Delta IgG values compared to patients with lesser Delta IgG values. Using Karl Pearson's correlation coefficient, no significant correlation exists between MRC scores at baseline or on 14th day to that of Delta IgG (difference in serum IgG levels at 14th day to that of the baseline) but however clinically difference exists with better clinical improvement in patients with higher Delta IgG levels on 14th day. Conclusion: Determining the Delta IgG values in the early phase (14 th day) of the disease course and using the value as a prognostic marker we can predict the clinical outcome early

***Keywords*---**Delta IgG, Guillain Barre Syndrome, prognostic, Immunoglobulin treatment.

Introduction

Guillain-Barré syndrome (GBS) is an acute onset immune-mediated disease affecting the peripheral nerve also its root (polyradiculoneuropathyy) (1). Previously termed Landrys paralysis(2) . Etiology is not completely understood, usually have good prognosis when it is detected and treated early(3) .It came to be known as a separate neurological entity during 1916. Now it's more common than poliomyelitis globally for acute flaccid paralysis Also, it is an emergency condition in neurology(1).

Seasonal variation present with more cases in the winter (3). Typically presents as rapidly progressing symmetrical limb weakness, may or may not have sensory disturbances, hyporeflexia or areflexia, and CSF analysis showing increased protein levels and WBC counts in normal range (albumino cytologic dissociation). For distinguishing it from infectious causes which have increased proteins and WBC counts. Patients usually give history of an antecedent infection or trauma. Symptoms reach nadir by four weeks after the start of symptoms. Many patients normally need hospitalization for therapy and monitoring. They may also develop dysautonomia in which they have sinus tachycardia and may also develop arrhythmias, fluctuating blood pressures, orthostatic hypotension, excessive sweating also bladder and GI disturbances. Around 5 percentage of them may develop respiratory failure and even death even after best therapies and ICU care. Diagnosis is mainly clinical, electrophysiological(EP) and CSF studies help to strengthen the diagnosis. GBS variants clinically have common key features and are distinguished based on EP studies (1) which includes the classic acute inflammatory demyelinating polyradiculoneuropathy (AIDP), EP studies reporting demyelination, variants having dysfunction or loss of neuronal axons which includes acute motor axonal neuropathy (AMAN) involving motor axons, and acute motor and sensory axonal neuropathy (AMSAN), involving both motor as well as sensory axons. AIDP being common in the European continent and North America constitutes around 90 percent of the cases, but recently done research in Italy it constituted about 58 percent of the cases. The axonal variants are commonly reported in Asia and South America, constituting around 30% to 70% of the total reportings. Another variant is the Miller Fisher syndrome (MFS) constituting 1-5% of cases from the West and 19–25% in the Asian continent(1).

Plasma exchange(PE) and intravenous immuno globulin(IVIG) have given evidence for faster recovery in GBS(4). IVIG treatment is comparatively costly but hospital stay duration is reduced(3).Other options include corticosteroids but have not shown benefit. Mortality of GBS is around 3%. Around 20 % patients have persisting neurological deficits and one half of these have severe disability (4). After a standard dose of IVIg treatment, GBS patients show a large variation in pharmacokinetics of IgG, which may be related to clinical outcome. The therapeutic dose of IVIg for GBS was empirically set at 2g per kg body weight, based mainly on the clinical experience in patients with immune deficiencies. Not all patients of GBS, however, show a good recovery after this standard dose. IVIg clearance may depend on disease severity and vary between individuals, implying that this dose may be suboptimal for some patients who might need DOSE adjustments for others the standard dose might be sufficient.

Aim:
The aim of the study is to determine the serum DELTA IgG values and evaluate its utility in the prognosis of Guillain Barre Syndrome after IVIG treatment.

Materials and Methods

- **STUDY SETTING**: The study was conducted in hospitals associated with KMC, Mangalore.
- **STUDY DESIGN**: Prospective Analytical study
- **STUDY POPULATION**: All diagnosed cases of Guillain barre syndrome receiving standard IVIg treatment.
- **STUDY DURATION**: September 2018 to August 2020.
- **INCLUSION CRITERIA**
  - All diagnosed cases of GBS >18 y receiving IVIg treatment
  - Patients who will give consent to participate in the study.
- **EXCLUSION CRITERIA:**
  Those patient**s** in whom the standard IVIg treatment protocol was not used .
- **DATA ANALYSIS**: Analysis will be done by using descriptive statistics
  Correlation was done by using Spearman‘s correlation co-efficient. A statistical package SPSS version 17.0 was used to do the analysis. P <0.05 was considered as significant.
- **DATA COLLECTION TOOL:** As per pre structured proforma

Study Methodology

Study was initiated after obtaining approval from Research Committee and Institutional Ethics Committee. The permission from the Medical Superintendent of KMC Hospital and DMO of GWH was obtained and consultation with experts were taken. At entry, all the diagnosed cases of GBS who receive a standard dose of IVIg, their total serum IgG levels were obtained immediately before and 2 weeks after the start of IVIg administration which were determined by turbidimetry also the GBS disability scores were determined at zero day , 2 weeks and 3 months after IVIg and MRC sum scores were determined at zero day and at 14 days after IVIg and related to Delta IgG values which is the difference in serum IgG levels between zero and 14 th day samples of IVIg treatment. Good outcome is defined as a GBS disability scale of ≤2, indicating the ability to walk unaided, at a follow-

up of 3 months. The GBS disability scale ranges from zero (no disability) to 6 (death) MRC sum score ranges from zero to sixty. Data was collected from GBS patients who received the standard IVIg dose and admitted in hospitals attached to KMC from 2018 to 2020

Budget and funding
Sample size approximately 40.
Total cost: 700×40=28000 approximately Twenty-eight thousand rupees only.

Sample Size: time bound study, approximately 40 cases

Implication

Identifying the prognosis of the disease at an early stage after the standard IVIg treatment might help patients who require dose adjustment of IVIg for their better prognosis and clinical outcome.

Knowledge GAP

After a standard dose of IVIg treatment, GBS patients show a large variation in pharmacokinetics of IgG, which may be related to clinical outcome. The therapeutic dose of IVIg for GBS was empirically set at 2g per kg body weight, based mainly on the clinical experience in patients with immune deficiencies. Not all patients of GBS, however, show a good recovery after this standard dose. IVIg clearance may depend on disease severity and vary between individuals, implying that this dose is suboptimal for some patients needing DOSE adjustments.

Results

Table 1: Descriptive statistics on the age wise distribution of the study participants

	N	Min	Max	Mean	SD
age	36	18	75	46.31	15.711
Valid N (listwise)	36				

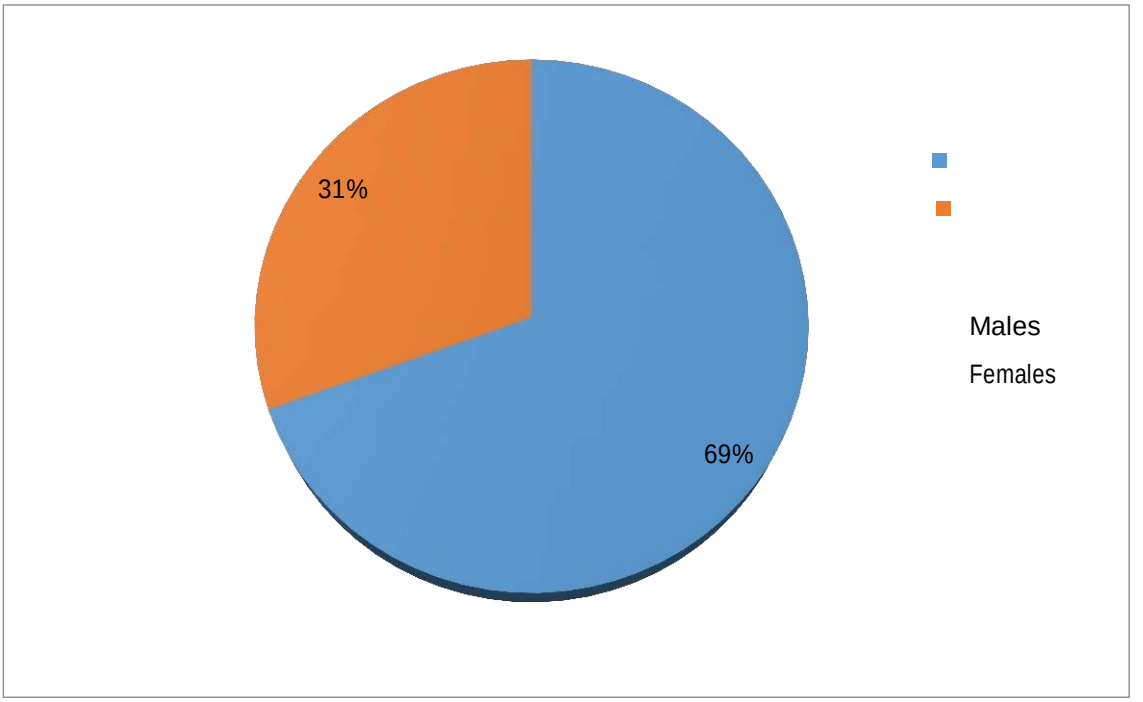
The mean age of the participants is 46.31 years with the standard deviation of 15.7 years Min age -18, Max-75 years.

Table 2: Age wise and gender wise distribution of the study participants

			gender		Total
			Males	Females	
	<20	Count	1	2	3
		% of Total	2.8%	5.6%	8.3%
	20-29	Count	3	0	3
		% of Total	8.3%	.0%	8.3%
		Count	5	1	6

Age in years	30-39	% of Total	13.9%	2.8%	16.7%
	40-49	Count	4	1	5
		% of Total	11.1%	2.8%	13.9%
	50-59	Count	6	6	12
		% of Total	16.7%	16.7%	33.3%
	60-69	Count	4	1	5
		% of Total	11.1%	2.8%	13.9%
	70-79	Count	2	0	2
		% of Total	5.6%	.0%	5.6%
Total		Count	25	11	36
		% of Total	69.4%	30.6%	100.0%

The age wise distribution of the patients in the sample showed a greater number of individuals 22 (61.1%) are in the age group of 40-69 years.



Graph 1: Pie chart representing gender wise distribution of study participants

Majority of the study participants were males (69%)

Table 3: Testing the significant difference in GBSD scores on the basis of gender (at baseline, 14th day and at 3months)

Test Statistic	gbsd_d0	gbsd_d14	gbsd_3month
Mann-Whitney U	113.500	127.500	123.500
Asymp. Sig. (2-tailed)	.362	.698	.599

Statistically no significant difference in GBSD scores observed based on gender at baseline, at 14th day and at 3 months(p>0.05)

Table 4: Testing the significant difference in MRC scores based on gender

Test Statistics	mrc_d0	mrc_d14
Mann-Whitney U	132.000	114.000
Asymp. Sig. (2-tailed)	.850	.417

Statistically no significant difference in MRC scores observed based on gender at baseline and at 14th day (p>0.05).
There were 25 males and 11 females in the sample. None of the baseline and follow up scores for MRC, GBSD varied between males and females.

Comparison of GBSD score between baseline and day14

Table 5: Descriptive Statistics

						Percentiles		
	N	Mean	SD	Min	Max	25th	50th (Median)	75th
gbsd_d0	36	3.64	.723	2	5	3.00	4.00	4.00
gbsd_d14	36	3.03	.654	2	4	3.00	3.00	3.00

Table 6: Ranks

		N	Mean Rank	Sum of Ranks
gbsd_d14 - gbsd_d0	Negative Ranks	25[a]	14.50	362.50
	Positive Ranks	3[b]	14.50	43.50
	Ties	8[c]		
	Total	36		

Table 7: Test Statistics

	gbsd_d14 - gbsd_d0
Z	-4.158[a]
Asymp. Sig. (2-tailed)	.000

Using Wilcoxon Signed rank test, statistically very high significant difference exists in GBSD scores at baseline and day 14 meaning there was improvement in GBSD scores on day 14 compared to baseline after the start of IVIG therapy with mean = 3.03 at day 14 compared to mean = 3.64 at baseline (p<0.001)

Comparison of GBSD score between baseline and 3month follow up

Table 8: Descriptive Statistics

						Percentile		
	N	Mean	SD	Min	Max	25th	50th (Median)	75th
gbsd_d0	36	3.64	.723	2	5	3.00	4.00	4.00
gbsd_3month	36	1.7500	.69179	1.00	3.00	1.0000	2.0000	2.0000

Table 9: Ranks

		N	Mean Rank	Sum of Ranks
gbsd_3month - gbsd_d0	Negative Ranks	35[a]	18.00	630.00
	Positive Ranks	0[b]	.00	.00
	Ties	1[c]		
	Total	36		

Table 10: Test Statistics

	gbsd_3month - gbsd_d0
Z	-5.254[a]
Asymp. Sig. (2-tailed)	.000

Using Wilcoxon Signed rank test, statistically very high significant difference exists in GBSD scores at baseline and follow up at 3month meaning there was improvement in GBSD scores at 3 months compared to baseline after the start of IVIG therapy with mean = 1.75 at 3 months compared to mean =3.64 at baseline($p<0.001$)

Comparison of MRC score at baseline and 14th day

Table 11: Descriptive Statistics

						Percentile		
	N	Mean	SD	Min	Max	25th	50th (Median)	75th
mrc_d0	36	37.50	9.539	12	54	34.00	38.00	44.00
mrc_d14	36	44.00	7.499	30	58	38.00	46.00	48.00

Table 12: Ranks

		N	Mean Rank	Sum of Ranks
mrc_d14 - mrc_d0	Negative Ranks	5[a]	17.90	89.50
	Positive Ranks	31[b]	18.60	576.50
	Ties	0[c]		
	Total	36		

Table 13: Test Statistics

	mrc_d14 - mrc_d0
Z	-3.843[a]
Asymp. Sig. (2-tailed)	.000

Using Wilcoxon Signed Rank test, statistically very high significant difference exists in MRC scores at baseline and day 14 meaning there was improvement in MRC scores on day 14 compared to baseline after the start of IVIG therapy with mean = 44 compared to mean=37 at baseline($p<0.001$)

The results revealed highly significant differences in the GBSD scores with a lesser score on follow up at 14 days and at 3 months from baseline and in MRC scores with a greater score at follow up at 14 days from baseline both of the sentences meaning there was clinical improvement in terms of both GBSD and MRC compared to baseline scores hence implying an improvement in muscle power on follow up compared to baseline.

Correlation between GBSD and Delta IgG

Table 14: Day 0

Correlations			
		gbsd_d0	Delta_IgG
gbsd_d0	Pearson Correlation	1	.110
	Sig. (2-tailed)		.523
	N	36	36

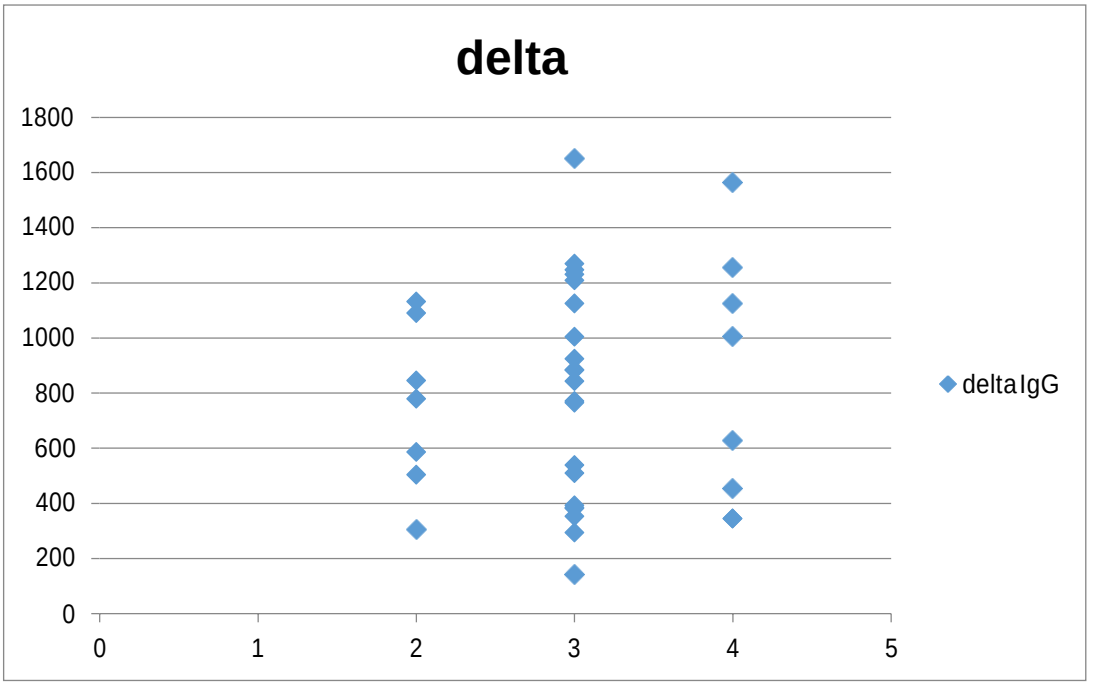
Table 14: Day 14

Correlations			
		Delta_IgG	gbsd_d14
Delta_IgG	Pearson Correlation	1	.076
	Sig. (2-tailed)		.659
	N	36	36

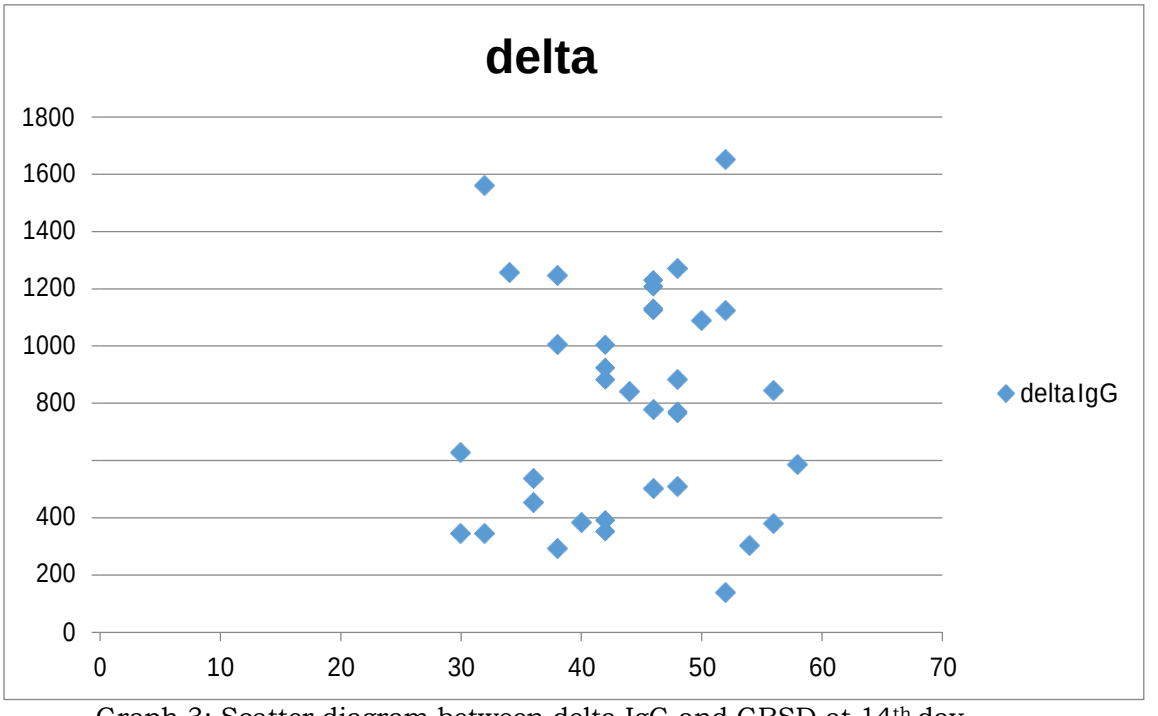
Table 14: After 3 months

Correlations			
		Delta_IgG	gbsd_3month
Delta_IgG	Pearson Correlation	1	-.431**
	Sig. (2-tailed)		.009
	N	36	36

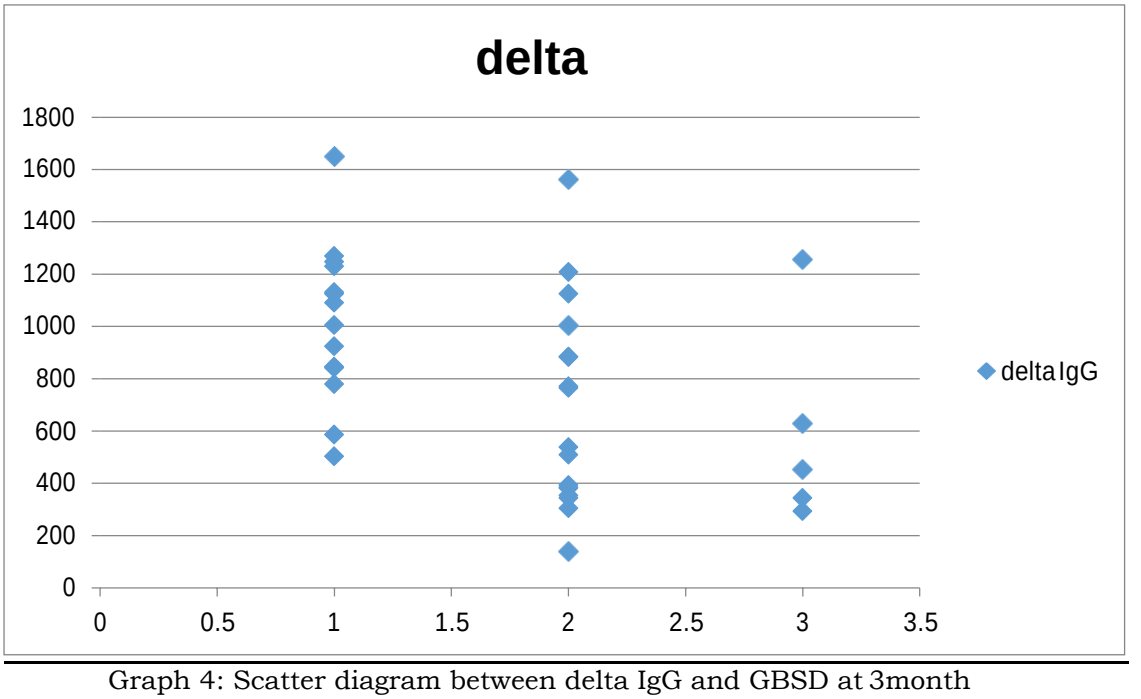
Using Karl Pearson's correlation coefficient, Negative correlation exists between GBSD scores at 3 months to that of Delta IgG (difference in serum IgG levels at 14th day to that of the baseline) and it is to be statistically highly significant meaning higher the Delta IgG lesser is the GBSD score at 3 months reflecting better clinical outcome with high Delta IgG values compared to patients with lesser Delta IgG values.



Graph 2: Scatter diagram between delta IgG and GBSD at 14th day



Graph 3: Scatter diagram between delta IgG and GBSD at 14th day



Graph 4: Scatter diagram between delta IgG and GBSD at 3month

Correlation between MRC sum score and Delta IgG

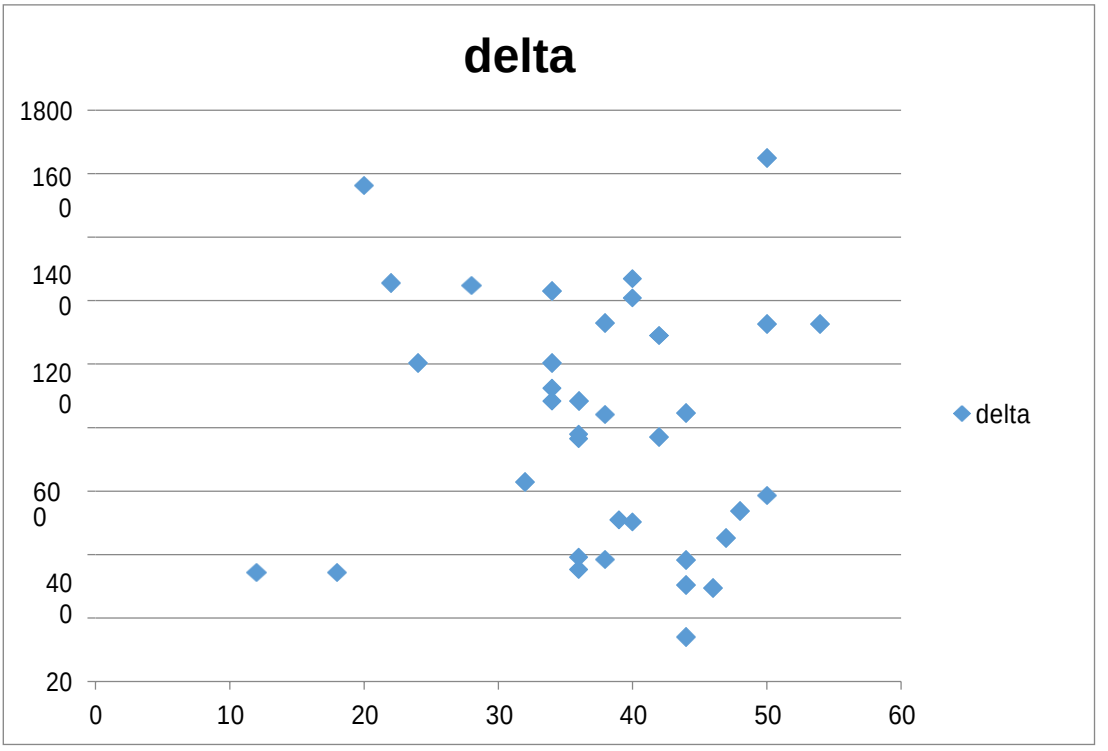
Table 15: Day 0

Correlations			
		Delta_IgG	mrc_d0
Delta_IgG	Pearson Correlation	1	-.065
	Sig. (2-tailed)		.708
	N	36	36

Table 16: Day 14

Correlations			
		Delta_IgG	mrc_d14
Delta_IgG	Pearson Correlation	1	.036
	Sig. (2-tailed)		.835
	N	36	36

Using Karl Pearson‘s correlation coefficient, no significant correlation exists between MRC scores at baseline or on 14th day to that of Delta IgG (difference in serum IgG levels at 14th day to that of the baseline) but however clinically difference exists with better clinical improvement in patients with higher Delta IgG levels on 14th day.



Graph 5: Scatter diagram between delta IgG and MRC sum at baseline

Discussion

Study was conducted among 36 patients with GBS who received intravenous immunoglobulin as treatment in KMC hospitals. Study was done to determine the correlation between Delta IgG (Difference of serum IgG values immediately before the start of intravenous immunoglobulin therapy i.e., zero day ,to that of serum IgG levels 14 days after start of treatment) with the clinical course and outcome of the patients at 14 days and at 3 months after initiation of treatment. All patients in this study received standard regime intravenous immunoglobulin infusion of 2g per kg body weight which resulted in considerable variation in the serum IgG levels(Delta IgG)between the patients. The Delta IgG levels were determined in all 36 patients about demographic characteristics, preceding illness, associated symptoms and complications developing during the stay. The variation in the Delta IgG was unrelated to sex, age, preceding illness. But patients with higher Delta IgG levels had better clinical course and outcome defined by MRC sum score at 14 days and GBSD score at 14 days and at 3 months after the initiation of IVIg treatment. Another study by Kuitwaard et al showed similar results that GBS patients with a low Delta IgG have a more severe clinical course and poor outcome after a standard dose of IVIg independent of other factors and a higher frequency of mechanical ventilation(48). Many potential reasons for the beneficial effect of IVIg in autoimmune diseases have been proposed. Possible mechanisms in GBS include: blockade of Fc receptors on macrophages preventing antibody-targeted attack on the Schwann cell membrane and myelin; regulation of autoantibodies or cytokines by anti- idiotypic or anti- cytokine antibodies in the

pooled immunoglobulin; up- regulation of the inhibitory Fc- gamma receptor IIB on B cells (43). down- regulation of B cell activating factor (44)and interference with the complement cascade or regulatory effects on T cells (45). According to an alternative hypothesis, the high concentrations of circulating immunoglobulin accelerate the breakdown of autoantibodies immunoglobulin G (IgG). Circulating IgG is picked up by specialised receptors, FcRn, on the endothelial cell surface, which endocytose the IgG and return it intact to the circulation. Excessive amounts of IgG exceed the capacity of the recycling system and divert the excess to the lysosomes where it is broken down (46). When the plasma IgG values reach 200% of its normal serum value the half-life of IgG decreases from 21 to 12 days (49).Hence it is possible to that this dose dependent clearance can be explained by saturation of the neonatal Fc receptor which was protecting the native IgG from degradation (46). The optimal dosage of IVIg treatment of GBS is unknown and the standa rd dosing regimen followed now was set based on experience of using IVIg in other autoimmune conditions. If the immune modulating property of IVIg is dose dependent then a low Delta IgG levels may lead to suboptimal immune suppression and modulation leading to more extensive or prolonged damaging of peripheral nerves and poor outcome.to support this there was a multicentre controlled trial comparing two IVIg regimes in one GBS patients were treated with 2.4 g per kg body weight dosing in 6 days and in other set of patients 1.2 g per kg body weight dosing in 3 days of IVIg was given which showed faster and better recovery in 2.4g per kg body weight dosing group (50).A case study suggested that GBS patients who show no sign of improvement clinically and deteriorate further a second dose of IVIg may be beneficial(51).This may indicate that in treatment of GBS a certain level of Delta IgG is needed for the substantial effect or that the subgroup of patient with low Delta IgG may improve with a higher dose of IVIg. In this study the decision to change the IVIg dose can be taken only after 2 weeks hence there is a possibility of delay to change the dosage of IVIg to improve outcome but also the time window in which IVIg treatment is still effective is unknown. IVIg treatment is used in many immune disorders and the pharmacokinetics of IVIg has been studied in heathy individuals as well as in patients which showed greater variation in the population studied and in patients greater variation can be expected as higher the disease activit y has more immune activation and more nerve damage hence may require higher consumption of IVIg (48).Furthermore, prospective studies are required to determine the role of serum IgG levels to optimize the IVIg treatment in GBS patients on individual basis.

Limitation

Study involves small sample size. However, inclusion of patients from different regions, races might help to improve the scope of the study. We observed practical difficulties when patients lost to follow up after treatment as the involved follow up also patients opting for plasma exchange over IVIg as therapy in view of financial issues especially in patients with low socio-economic backgrounds reduced the sample size.

Conclusion:

Based on our study by determining the Delta IgG values in the early phase(14 th day) of the disease course and using the value as a prognostic marker we can predict the clinical outcome early and can help making changes to the conventional standard dose regime based on patients requirement for bringing in better clinical outcome.

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