

PREDICTORS OF RESPONSE TO PLASMAPHERESIS IN AUTOIMMUNE NEUROPATHIES

By

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ABSTRACT

Background: Immune-mediated neuropathies represent a significant portion of cases encountered by neurologists. The scope of responsive neuropathies, the extent of response to plasmapheresis and its predictors varies widely.

Objective: To recognize predictors of response to plasmapheresis in autoimmune-neuropathies.

Patients and Methods: Seventy-six subjects; 61 Guillain-Barre syndrome (GBS) patients and 15 chronic inflammatory demyelinating polyneuropathy (CIDP) patients were recruited and evaluated using Medical Research Council sum score (MRCSS) and Modified Neuropathy Disability Score (NDS); on admission, 2 weeks and 3 months after six session of plasmapheresis. Different clinical, laboratory and neurophysiological variables were evaluated as possible predictors of response.

Results: Of 61GBS patients, after 3 months, 41% (n=25) of them were poor-responders to plasmapheresis (<50% increase in MRCSS), and 59% (n=36) were good-responders. Older age, higher MRCSS on admission, lower NDS on admission, cyto-albuminous dissociation, electro-physiological evidence of axonal nerve affection and low NLR were predictors for poor response to plasmapheresis in GBS patients. Of 15 CIDP patients, after 3 months, 53.3% (n=8) of them were poor-responders to plasmapheresis (< 30% increase in MRCSS), and 46.7% (n=7) were good-responders. Higher MRCSS on admission, low CMAP amplitude, low MCV and long time between onset of the health problem and start of plasmapheresis were predictors for poor response to plasmapheresis in CIDP patients.

Conclusion: Response to plasmapheresis in autoimmune neuropathies is variables and depends on several factors that can predict it.

Keywords: Guillain–Barré, Demyelinating Polyneuropathy, Prognosis, Plasmapheresis.

INTRODUCTION

Autoimmune neuropathies are an etiologically heterogeneous entity with variable clinical presentations. The common autoimmune neuropathies include; Guillain–Barré Syndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Multifocal Motor

Neuropathy with conduction block and Polyneuropathies associated with IgM monoclonal gammopathies (*Shimizu et al., 2019*).

GBS is a collection of clinical syndromes that presents as an acute inflammatory polyradiculoneuropathy; distinguished by an acute onset, rapid

progression, symmetric muscle weakness, unstable walking, and hypo- or areflexia. Some types of it may affect exclusively the cranial nerves or had pure motor involvement and axonal injury (*Willison et al., 2016*).

Based on several studies generating class I evidence, plasmapheresis has been established as effective treatment in GBS therapy (type A recommendation) (*Hugh et al., 2016*).

CIDP is the commonest chronic immune-mediated inflammatory polyneuropathy, and includes many subtypes that belong to the spectrum of causally treatable neuropathies (*Lehmann et al., 2019*).

The term (CIDP) has been used to distinguish patients with a chronically progressive or relapsing symmetric sensorimotor manifestations with cytoalbuminous dissociation and interstitial and perivascular endoneuronal infiltration by lymphocytes and macrophages (*Jeffrey et al., 2020*).

There is class I evidence that plasmapheresis is superior to sham treatment in CIDP, so, recommended in the treatment of CIDP (type A recommendation) (*Dyck and Tracy, 2018*).

Most of Multifocal motor neuropathy patients didn't benefit from plasmapheresis in different studies, and some reported severe clinical worsening (class IV evidence, type U recommendation) (*Shimizu et al., 2019*).

Response to treatment with plasmapheresis in autoimmune neuropathies is variable. We believe that predicting that response and identifying possible predictors is vital, particularly if

different choices are available. This gains a greater importance in low resource circumstances particularly that plasmapheresis is a costly procedure and is not without complications.

The aim of this study was to recognize predictors of response to plasmapheresis in two entities of autoimmune-neuropathies; GBS and CIDP.

PATIENTS AND METHODS

This study has been designed as analytical prospective observational study, and was conducted at Al-Azhar University Hospitals and Neurology Department, Nasser Institute Hospital within the period between November 2015 and Jan 2020.

The study included patients were diagnosed with GBS according to the diagnostic criteria of *Van Doorn (2013)* and *van den Berg et al. (2014)*. Patients were diagnosed with CIDP, using the European Federation of Neurological Societies/Peripheral Nerve Society Diagnostic Criteria (EFNS/PNS), from all ages of both genders. Convenient sample of seventy-six (76) patients have been recruited.

The requirements of Al-Azhar University Ethics Committee were fulfilled, and an informed written consent had been obtained from every patient before participating in the study.

At time of admission, all cases were subjected to: medical research council sum score (MRCSS) for muscle strength, and modified neuropathy disability score (NDS) for sensory functions, nerve conduction studies, routine laboratory

work up, and other laboratory/imaging investigations whenever needed.

Plasmapheresis was applied for patients: one session every other day over two weeks (6 sessions as a standard). Plasmapheresis was accomplished through centrifuge-based platforms; "Cobe-Spectra" and "Fresenius COM.TEC" device series, with appropriate patient preparation, monitoring, symptomatic adjustments and exchange technique. Two weeks after starting plasmapheresis, all cases were subjected to MRCSS and NDS. That was repeated after three months.

Each of The GBS patients group and CIDP patient group was divided into two groups: Group A: Good-responders to treatment ($\geq 50\%$ [30% in CIDP], increase in MRCSS, and/or decrease in NDS), and Group B: Poor-responders to treatment ($< 50\%$ [30% in CIDP] increase in MRCSS and/or decrease in NDS).

For each scale, we compared and analyzed the two groups as regard

demographic, clinical, biochemical and neurophysiological characteristics to recognize predictors of response.

Statistical analysis:

Analytical statistics for the association between different variables and the outcome variables were done using independent T test for normally distributed numerical variables (mean and standard deviation) and the non-parametric test Mann Whitney U test for the non-normally distributed numerical variables (median and interquartile range). The association between categorical variables (frequency and relative frequency) and different outcome variables was done using Chi square test and Fisher's exact test. Binary logistic regression was used to study the association between predictive variables and the outcome variable in GBS patients. P-value less than (0.05) were considered significant.

RESULTS

Sixty-one GBS patients; 63.9% (n=39) of them were males and 36.1% (n=22) were females. The age distribution ranged from 5 to 80 years; the mean \pm SD was 40.5 ± 17.2 years. 44.3% (n= 27) of GBS patients had history of antecedent infection, 31.1% (n= 19) had cranial nerve affection, and 77% (n= 47) had Cyto-albuminous Dissociation. Only 4.9% (n= 3) of them needed artificial ventilation. Also, 1.6% (n= 1) had autonomic symptoms. The neutrophil-lymphocyte

ratio (NLR) ranged from 1.1 to 3.7, mean value \pm SD was 2.4 ± 1 . The ESR ranged from 5 to 45, mean value \pm SD was 23.7 ± 9.6 . And CRP ranged from 2 to 52, mean value \pm SD was 5.5 ± 6.3 . MRCSS on admission ranged from 2 to 48, mean value \pm SD was 27.1 ± 15.9 . By electro-diagnosis, 39.3% (n=24) had evident demyelination and 39.3% (n=24) had axonal changes. The remaining percent had mixed pattern of affection (**Table 1**).

Table (1): MRCSS in GBS

MRCSS(GBS) Parameters	According to percent of increase in					P-value
	Median at 2 w		P-value	Median at 3 m		
	Poor-responders 42.6% (n=26)	Good-responders 57.4% (n=35)		Poor-responders 41% (n=25)	Good-responders 59% (n=36)	
NDS on admission	6.00	8.00	0.015	6.00	7.00	0.015
MRCSS on admission	48.00	12.00	<0.001	48.00	12.00	<0.001
NLR on admission	3.01	1.88	0.246	3.28	1.88	0.232

According to percent of decrease in NDS, GBS patients were divided into good and poor responders and analysed

different variants assumed to be possible predictors of response to plasmapheresis (Table 2).

Table (2): NDS at 2 weeks in GBS

NDS at 2 weeks (GBS)		Poor-responders 86.9% (n=53)	Good-responders 13.1% (n=8)	P-value
Parameters				
Age (years) (Median)		45.00	29.50	0.035
NDS on admission (Median)		6.00	8.00	<0.001
MRCSS on admission (Median)		24.00	12.00	0.002
NLR on admission (Median)		1.96	3.42	0.005
NCS on admission N (%)	Demyelinating	17 (32.1%)	7(87.5%)	0.012
	Axonal	24 (45.3%)	0(0.0%)	
	Mixed	12 (22.6%)	1(12.5%)	
Cyto-alb. Dissociation	Absent	917.0%	562.5%	0.012
	Present	44(83.0%)	3(37.5%)	

We found that the variables showed statistically significant difference between the two groups were the median age was significantly higher in poor-responders group (NDS at 2w), The NDS on admission was lower in poor responders (NDS at 2w – MRCSS at 2w, 3m), The MRCSS on admission was higher in poor-responders (NDS at 2w – MRCSS at 2w, 3m), more patients of the non-responders group had Cyto-albuminous Dissociation (NDS at 2w), Increase in percent of patients who had electro-diagnostic evidence of predominantly axonal pattern of neuropathy within the poor-responder group (NDS at 2w) and the Neutrophil Lymphocyte Ratio (NLR) values were significantly lower in poor-responders group (NDS at 2w).

A logistic regression analysis was done to examine the association between different variables and the occurrence of more than 50% improvement in the MRCSS score. Significant variables in the bivariate analysis were included in the model. After controlling for other variables, the only significant predictor of more than 50% improvement in the MRCSS score are MRCSS on admission (OR=0.92). The higher the MRCSS at admission the lower the probability of occurrence of more than 50% improvement in the MRCSS score.

Our study did not notice any statistically significant distinction between poor-responder and good responder groups as regard time to start treatment, the need for ventilator at nadir, history of preceding infection, gender difference,

cranial nerve affection and the presence of autonomic symptoms.

We recruited fifteen CIDP patients; 63 percent 60% (n=9) of them were females and 40% (n=6) of them were males. The distribution of the ages of group was ranging from 20 to 71 years old; the mean age \pm SD was 47.4 ± 14.07 years.

In the CIDP patient group; the MRCSS on admission ranged from 14 to 48 with mean \pm SD was 32.93 ± 10.33 . And NDS values ranged from 2 to 10 with mean \pm SD was 5.73 ± 1.98 . We also found 40% (n= 6) of them had Cyto-albuminous Dissociation.

The time period between onset of symptoms and starting treatment ranged

from 2 to 60 months with the mean value \pm SD was 16.67 ± 18.2 . Moreover, 20% (n=3) of patients received other Immunosuppressive therapy before starting plasmapheresis with poor response and 60% (n=9) of patients received steroid treatment, from them 77.78% (n=7) responded poorly to steroid therapy.

According to percent of increase in MRCSS and percent of decrease in NDS, we divided GBS patients into good and poor responders and analysed different variants assumed to be possible predictors of response to plasmapheresis (**Table 3**).

Table (3): MRCSS and NDS in CIDP

MRCSS and NDS (CIDP) Parameters	Median at 2 w		P-value	Median at 3 m		P-value
	Poor-responders 66.7% (n=10)	Good-responders 33.3% (n=5)		Poor-responders 53.3% (n=8)	Good-responders 46.7% (n=7)	
MRCSS on admission	41	28	0.04	42	28	0.002
CMAP amplitude Ulnar	1	3.6	0.078	0.9	2.2	0.04
MCV Ulnar	33	50	0.026	28.4	50	0.075
time from Onset of symptoms to start of PE (in months)	15	3	0.04	31	2	0.013

We found that the variables showed statistically significant difference between the two groups were the patient score on MRCSS was significantly higher among the poor-responder group (MRCSS at 2w & 3m), CMAP amplitude for ulnar nerve were significantly lower among the poor-responder group (NDS at 3m), MCV for ulnar nerve were significantly lower among the non-responder group(NDS at 3m) and the time from onset of symptoms till start of plasmapheresis were

significantly higher among the poor-responders (NDS at 2w & 3m).

In our study, we could not find any statistically significant difference between the good-responder group and the poor-responder group of CIDP patients as regard; NDS on admission, NLR on admission, Sex, presence of muscle atrophy on admission, Cyto-albuminous Dissociation, Steroid Exposure and Immunosuppressive Drug Exposure.

DISCUSSION

In our study, older age was predictor for poor response to PP in GBS patients. This prophetic ability has been confirmed through the study of *Willison (2016)*.

In our study, higher MRCSS and lower NDS on admission were predictor for poor response (<50% change in clinical score) to PP in GBS patients. Our results confirmed that the poorer the clinical score, the more benefit can the patient get from plasmapheresis, and patients who had better scores on clinical scores will not get much benefit from this procedure. This was consistent with *Verboon (2017)* who doubted treatment efficacy in patients. This was consistent with *Hughes et al. (2014)* and *Chevret et al. (2017)*.

In our study, cyto-albuminous dissociation was predictor for poor response to plasmapheresis in GBS patients. *Zhang et al. (2018)* reported the contrary. However, in our study this significance was evident solely on NDS at period of 2 weeks and was not present on the same scale after three months.

In our study, electrophysiological proof of nerve axonal affection was predictor for poor response to PP in GBS patients. This ability has been confirmed in a similar study by *Zhang et al. (2018)*.

In our study, low NLR was predictor for poor response to PP in GBS patients. This ability has been confirmed in similar studies; *Sahin et al. (2017)* and *Hashim et al. (2020)*.

Our study did not notice any statistically significant distinction between groups as regard time to begin treatment. That was against the finding of *Chevret et al. (2017)* and *Prasad et al. (2017)*. This

may be explained as 86.9% of our GBS patient group started treatment early within one week.

Our study did not notice any statistically significant distinction between groups as regard the need for ventilator, preceding infection and autonomic symptoms. That was against the finding of *Zhang et al. (2018)*. This difference is probably due to logistic factors in our study, as there was limitation in admitting critically ill patients due to shortage in ICU beds, so the percent of patients who needed ventilators or had dysautonomic findings was small in our study. Also, only 4.9% of our patients needed ventilation, and only 1.6% had autonomic symptoms. Non-specified type of infection in our study may justify our results as preceding upper respiratory infection is related to better prognosis, while GIT infection is related to poor prognosis (*Kuwabara, 2011*).

Our results showed insignificant difference between groups as regard gender, cranial nerve affection which was similar to the results of *Prasad et al. (2017)*.

In our study, higher MRCSS was predictor for poor response to plasmapheresis in CIDP patients. That was not the case in the study introduced by *Lehmann (2019)* who reported that MRC scale was not significantly different between the patients with remission and the others.

Wu et al. (2015) reported disability at the time of diagnosis was the strongest predictor of poor outcome. However, our study confirms the predictor value for percent of improvement in response to

plasmapheresis not long term general outcome.

In our study, lower CMAP and MCV amplitude was predictor for poor response to PP in CIDP patients. This predictive ability has been confirmed in the stud of *Rajabally et al. (2011)*.

In our study, longer disease duration before plasmapheresis was predictor for poor response to plasmapheresis in CIDP patients. This predictive ability has been reported by *Lehmann (2019)*.

In our study, we could not notice any statistically significant distinction between the good-responder group and the poor-responder group of CIDP patients as regard; Age, NDS on admission, NLR on admission, Sex, presence of muscle atrophy on admission, Cyto-albuminous Dissociation, Steroid Exposure and Immunosuppressive Drug Exposure. This was consistent with report of *Lehmann (2019)*.

Regression analysis couldn't be performed for the CIDP patient group in our study as the sample size was unsuitable for satisfying the assumption required for regression analysis.

CONCLUSION

Autoimmune neuropathies (GBS & CIDP) are responsive to plasmapheresis in variable degrees. Older age, higher MRCSS on admission, lower NDS on admission, cyto-albuminous dissociation, electrophysiological evidence of axonal affection and low NLR were predictors for poor response to plasmapheresis in GBS patients. Higher MRCSS on admission, low CMAP amplitude, low MCV and long time between onset of symptoms and begin of plasmapheresis were predictor

for poor response to plasmapheresis in CIDP patients.

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منبئات الاستجابة للعلاج بفصل البلازما في الاعتلال المناعي للأعصاب الطرفية

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خلفية البحث: يمثل الاعتلال المناعي للأعصاب الطرفية نسبة معتبرة من الحالات التي تواجه أطباء الأعصاب، وتتنوع هذه الحالات في مدى استجابتها للعلاج بجلست فصل البلازما، كما تتنوع المنبئات لمدى هذه الاستجابة.

الهدف من البحث: التعرف على منبئات الاستجابة لجلسات فصل البلازما في الاعتلال المناعي للأعصاب الطرفية.

المرضى وطرق البحث: اشتملت الدراسة على واحد وستين (61) مريضا مصابين بمتلازمة جيلان باريه، وخمسة عشر (15) مريضا مصابين بمرض الالتهاب المزمن للأعصاب الطرفية المصحوب باعتلال غمد المايلين. وتم تقييم حالتهم بواسطة مقياس الكلية الطبية الملكية المجمع للقوة العضلية و مقياس الإعاقة المعدل لاعتلال الأعصاب قبل بداية العلاج ثم بعد أسبوعين من بداية العلاج والخضوع لستة جلسات فصل بلازما، ثم بعد ثلاثة شهور. وتم تقييم عدد من المتغيرات الإكلينيكية والمعملية والفيسيولوجية كمنبئات محتملة للاستجابة للعلاج.

نتائج البحث: أظهرت الدراسة أن 59% من مرضى متلازمة جيلان باريه تحسنا تحسنا ملحوظا (كانة نسبة الزيادة على مقياس الكلية الطبية الملكية المجمع للقوة العضلية $\leq 50\%$)، وأن 41% منهم لم يتحسنوا بشكل كبير (كانة نسبة الزيادة على المقياس $> 50\%$)، وكانت بعض العوامل ذات قيمة تنبؤية بهذا الضعف في الاستجابة للعلاج، ومن هذه العوامل: ارتفاع السن، وانخفاض درجة المريض على مقياس الإعاقة المعدل لاعتلال الأعصاب، وارتفاع درجة المريض على مقياس الكلية الطبية الملكية المجمع للقوة العضلية، ووجود كميات كبيرة من البروتين في عينات السائل الشوكي مقارنة بانعدام وجود لخلايا، ووجود أدلة من خلال أبحاث فيسيولوجيا الأعصاب تؤكد الإصابة باعتلال المحور العصبي،

وانخفاض نسبة كرات الدم البيضاء المتعادلة إلى نسبة كرات الدم الليمفية. كما أظهرت الدراسة أن 46.7% من مرضى التهاب المزمّن للأعصاب الطرفية المصحوب باعتلال غمد المايلين تحسّنوا تحسّنا ملحوظا (كانة نسبة الزيادة على مقياس الكلية الطبية الملكية المجمع للقوة العضلية $\leq 30\%$)، وأن 53.3% منهم لم يتحسّنوا بشكل كبير (كانة نسبة الزيادة على المقياس $> 30\%$)، وكانت بعض العوامل ذات قيمة تنبؤية بهذا الضعف في الاستجابة للعلاج، ومن هذه العوامل: انخفاض درجة المريض على مقياس الإعاقة المعدل لاعتلال الأعصاب، وارتفاع درجة المريض على مقياس الكلية الطبية الملكية المجمع للقوة العضلية، ووجود أدلة من خلال أبحاث فيسيولوجيا الأعصاب تؤكد انخفاض قيمة جهد الحركة المركبة وسرعة التوصيل في العصب، وارتفاع المدة الزمنية بين بداية ظهور أعراض المرض وبين تلقي العلاج.

الاستنتاج: يوجد تباين في مدى الاستجابة للعلاج بجلسات فصل البلازما في حالات الاعتلال المناعي للأعصاب الطرفية، ويعتمد هذا التباين على عدد من العوامل التي يمكنها التنبؤ به.