

The prognostic value of demyelinating electrophysiologic findings and cerebrospinal fluid protein levels in acute inflammatory demyelinating polyneuropathy

O valor prognóstico dos achados eletrofisiológicos desmielinizantes e os níveis de proteína do líquido cefalorraquidiano na polineuropatia desmielinizante inflamatória aguda

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ABSTRACT

Background: Guillain-Barre syndrome is an acute immune-mediated polyneuropathy characterized by rapidly evolving symptoms and disability. Cerebrospinal fluid analysis and electrophysiological studies are crucial in the diagnosis of this syndrome. **Objective:** To evaluate the prognostic value of the type and number of demyelinating findings and cerebrospinal fluid protein levels in patients with acute inflammatory demyelinating polyneuropathy. **Methods:** We retrospectively analyzed electrophysiological data and cerebrospinal fluid of 67 consecutive patients with acute inflammatory demyelinating polyneuropathy from Istanbul, Turkey (2011-2019) studied \leq 24 hours post-onset. **Results:** The patients who met a higher number of demyelinating criteria had increased disability scores in the first day and first month, and higher cerebrospinal fluid protein levels were correlated with worse prognosis both on the first day and the first month. However, the disability scores did not correlate with any single specific criterion, and no significant correlation was found between the number of satisfied criteria and cerebrospinal fluid protein levels. **Conclusions:** The number of demyelinating criteria that are met and high cerebrospinal fluid protein levels at the disease onset may be valuable prognostic markers. More systematic studies conducted with serial nerve conduction studies are required to highlight the roles of the suggested criteria in clinical practice.

Keywords: Guillain-Barre Syndrome; Prognosis; Electromyography.

RESUMO

Introdução: A síndrome de Guillain-Barré é uma polineuropatia imunomediada aguda caracterizada por sintomas e incapacidade em rápida evolução. A análise do líquido cefalorraquidiano e os estudos eletrofisiológicos são cruciais no diagnóstico dessa síndrome. **Objetivo:** Avaliar o valor prognóstico do tipo e número de achados desmielinizantes e dos níveis de proteínas do líquido cefalorraquidiano em pacientes com polineuropatia desmielinizante inflamatória aguda. **Métodos:** Analisamos retrospectivamente dados eletrofisiológicos e líquido cefalorraquidiano de 67 pacientes consecutivos com polineuropatia desmielinizante inflamatória aguda de Istanbul, Turquia (2011-2019), estudados \leq 24 horas após o início. **Resultados:** Os pacientes que atenderam a um número maior de critérios desmielinizantes apresentaram escores de incapacidade aumentados no primeiro dia e no primeiro mês, e níveis mais altos de proteína do líquido cefalorraquidiano foram correlacionados com pior prognóstico no primeiro dia e no primeiro mês. No entanto, os escores de incapacidade não se correlacionaram com nenhum critério específico e não foi encontrada correlação significativa entre o número de critérios satisfeitos e os níveis de proteína do líquido cefalorraquidiano. **Conclusões:** O número de critérios desmielinizantes atendidos e altos níveis de proteína no líquido cefalorraquidiano no início da doença podem ser marcadores prognósticos valiosos. Estudos mais sistemáticos conduzidos com estudos de condução nervosa em série são necessários para destacar os papéis dos critérios sugeridos na prática clínica.



Palavras-chave: Síndrome de Guillain-Barré; Prognóstico; Eletromiografia.



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INTRODUCTION

Guillain-Barre syndrome (GBS) is an acute immune-mediated polyneuropathy characterized by rapidly evolving symptoms, which are usually ascending symmetrical weakness or paralysis, and areflexia or hyporeflexia. The symptoms reach their maximum severity up to four weeks^{1,2}. Acute motor axonal neuropathy and acute inflammatory demyelinating polyneuropathy (AIDP) are the two major subtypes of GBS^{1,3,4}. At least 90% of GBS patients present with AIDP in Western countries, while the frequency decreases in South America and China^{1,4}. An immune response induced by infections causes myelin and axon damage or nerve conduction blockages⁵.

Cerebrospinal fluid (CSF) analysis and electrophysiological studies are crucial in the diagnosis of GBS⁶. Total CSF protein levels indicate active myelin breakdown and increased antibody depositions secondary to the inflammation⁷. Additionally, elevated CSF protein levels have been shown to be surrogate markers of injury that correlate with progression and disability related to GBS⁸.

In clinical practice, nerve conduction studies (NCS) still provide the best diagnostic modalities, despite the new histopathological and radiological techniques available for GBS⁹. Some specific electrodiagnostic features, such as increased distal motor latencies, markedly decreased peripheral nerve conduction velocities, abnormal F-waves, and nerve conduction blocks can appear in the early stages of AIDP. However, the exact timing of the onset of electrophysiological findings has not been precisely determined^{10,11}.

Potential GBS prognostic determinants have been assessed in several studies in recent years^{12,13}. Most of these studies evaluated muscle strength at admission, presence of facial or bulbar muscle involvement, rapidly progression, preceding diarrhea, compound muscle action potential amplitude, and mechanical ventilation requirement as negative predictors of the outcome of GBS^{12,14}. Only a few studies have reported the association of electrophysiological abnormalities, CSF proteins levels, and prognosis^{6,13,15}.

The purpose of our study was to evaluate the prognostic value of the type and number of demyelinating electrophysiologic findings on NCS and CSF protein levels in patients with AIDP.

METHODS

This retrospective study was performed using electronic medical records from Bezmialem Vakıf University, between January 2011 and June 2019. The records of 166 GBS patients aged between 17 and 84 years were analyzed, and only patients who had disability scores at first day and first month of the symptom onset day and who had CSF analysis and electrophysiological findings within the first 24 hours

(16 to 24 hours) were included for subsequent analysis. Of the 166 records, 32 of them had no CSF or incomplete CSF results. Other 12 patients had no record of having had an electrophysiological study. Of the remaining 122 records that had both electrophysiological studies and CSF results, only 86 patients had both studies performed within 24 hours of each other. Exclusion criteria for this study were as follows: neurologic deficits that could affect the assessment of GBS severity, other subtypes of GBS, autoimmune disease, hypertension, diabetes, heart failure, history of vasculitis, thyroid disease, kidney dysfunction, local and systemic infection, and liver disease. Finally, 67 patients for whom the diagnosis of AIDP was verified in serial electrophysiological investigations were enrolled after considering the exclusion criteria. These serial investigations were conducted within one to four weeks after symptom onset. The study was approved by the Human Ethics Committee of Bezmialem Vakıf University (in 2018, protocol 54022451-050.05.04)

With a clinical finding of progressive weakness and areflexia, GBS diagnosis was established using the criteria suggested by Asbury and Cornblath¹⁶. Clinical features, including age, gender, detailed neurological examination, CSF analysis, and electrophysiological studies were assessed for all patients.

Hughes disability score (HDS) was evaluated to assess the prognosis of AIDP patients at the end of the first day and the first month. This scale is outlined as follows: 0 — healthy, 1 — minor symptoms and capable of running, 2 — able to walk 5 m or more without assistance but unable to run, 3 — able to walk 5 m across an open space with help, 4 — bedridden or chair-bound, 5 — requiring assisted mechanical ventilation for at least part of the day, and 6 — death¹⁷.

Lumbar puncture for CSF examination was performed with the patient in lateral decubitus. The normal range in our laboratory was 15 to 45 mg/dL for CSF protein levels. The NCS were applied using a Dantec Keypoint electromyograph (Natus, Copenhagen, Denmark). Motor (median, ulnar, peroneal, and tibial) and sensory (median, ulnar, superficial peroneal, and sural) NCS were performed on both sides. Amplitudes, distal latencies, nerve conduction velocities, H reflexes, and F-waves were measured. We used David Cornblath's 1990 demyelinating criteria for AIDP¹⁸. The patients were categorized according to the presence of prolonged distal latencies, slowed conduction velocities, abnormal F-waves, temporal dispersion, and/or complete or partial conduction block. Additionally, the patients were divided into three groups (none, one criterion, and two or more criteria). The CSF protein levels and HDS scores were evaluated between groups and according to the number of satisfied criteria.

Statistical analysis

Data were transferred to the IBM SPSS Statistics 22 program (SPSS, Inc., Chicago, IL, USA) for analysis. The mean,

lowest and highest medians, standard deviation, frequency, and ratio values were computed from the data. The Kolmogorov-Smirnov test was used to measure variable distribution. Quantitative independent data were analyzed by Mann-Whitney U and Kruskal-Wallis tests. The dependent quantitative data were assessed through Wilcoxon's test. A chi-squared test was used for the qualitative independent data analysis. The level of significance was set at $p < 0.05$.

RESULTS

After applying inclusion and exclusion criteria, a total of 67 AIDP patients were included in the study, with a mean age of 51.6 ± 18.4 (17–84), of whom 39 were males (58.2%) and 28 were females (41.8%). Two patients had recurrent GBS. One patient died at the end of the first month. Sixty-two patients were treated with intravenous immunoglobulin (IVIg), and due to its ineffectiveness, plasma exchange was applied to five patients after IVIg. Five of the patients were only followed with supportive treatment.

The mean HDS score was 2.9 ± 1.1 on the first day and 1.8 ± 1.1 at the end of the first month. Of these patients, 15 met only one, 6 met 2, 11 met 3, and the remaining 22 met four of the Cornblath demyelination criteria¹⁸. Thirteen of these patients met none of the demyelination criteria (Table 1).

The electrophysiological findings were then compared with the patients' HDS scores and CSF protein levels. Thirty-nine patients had prolonged distal latencies in

two or more nerves and had an average CSF protein level of 115.9 mg/dL. Thirty-one patients had slowed conduction velocities in two or more nerves with an average CSF protein level of 103.1 mg/dL. Forty-five patients had two or more abnormal F-waves, with an average CSF protein level of 102.1 mg/dL. Thirty-three patients exhibited temporal dispersion and/or complete or partial conduction blocks with an average CSF protein level of 110 mg/dL.

No significant differences were detected in terms of age, gender, CSF protein levels, HDS scores for the first day and the first month, and HDS intragroup changes as indicated by the presence or absence of any of the demyelinating criteria ($p > 0.05$). The HDS scores of the first month were significantly lower than those on the first day for all the groups ($p < 0.01$), as seen in Table 2.

Similarly, when patients were divided into three groups (none, one criterion, and two or more criteria), no significant differences were found in terms of CSF protein levels, HDS scores after the first day and the first month, and HDS intragroup changes ($p > 0.05$). The HDS scores of the first month were significantly lower than those of the first day for all three groups ($p < 0.01$), as in Table 3.

Finally, patients were evaluated based on the number of satisfied criteria. No significant correlation was found between the number of satisfied criteria and CSF protein levels ($p > 0.05$). Patients who met more criteria had higher HDS scores on the first day and first month ($p = 0.049$; $p = 0.009$), and higher CSF protein levels were correlated with worse prognosis, both on the first day and the first month ($p = 0.006$; $p = 0.016$), based on Table 4.

Table 1. Patients' evaluated data.

	Min–Max	Median	Mean \pm SD/n (%)
Age	17–84	55	51.6 \pm 18.4
Gender	Female		28 (41.8)
	Male		39 (58.2)
CSF protein	19–277.1	96.1	111.4 \pm 68.6
HDS score 1st day	1–5	3	2.9 \pm 1.1
HDS Score 1st month	0–6	2	1.8 \pm 1.1
Slowed conduction velocities (+)			31 (46.2)
Conduction block (+)			33 (49.2)
Prolonged distal latencies (+)			39 (58.2)
Abnormal F-waves (+)			45 (67.1)
Number of criteria	None		13 (19.4)
	1 Criteria		15 (22.3)
	2 Criteria		6 (8.9)
	3 Criteria		11 (16.4)
	4 Criteria		22 (32.8)

CSF: cerebrospinal fluid; HDS: Hughes disability scale; SD: standard deviation.

DISCUSSION

In the current study, we examined the role of the type and number of demyelinating electrophysiologic findings and CSF protein levels as prognostic markers of outcome in AIDP patients. Since previous studies reported these investigations have evolved over the course of the disease^{19,20}, the first day (the first 16 to 24 hours) was specifically included in order to investigate prognosis correlations.

The final prognosis prediction is important for a successful treatment of GBS because of the clinical course variability. Early predictions enable clinicians to provide proper and cost-effective treatments. Many studies have investigated the prognostic determinants of GBS^{6,8,12,13,14}. We evaluated the clinical course at the end of the first day and first month, and we found that patients who satisfied a higher number of demyelinating criteria and exhibited higher CSF protein levels had increased disability scores in the first day and first month. This study stands out by showing such correlation in a relatively large patient cohort.

Total CSF protein levels show the deposition degree of active myelin breakdown products, complements, and

Table 2. Correlation analysis of specific demyelinating criteria, cerebrospinal fluid protein levels, and Hughes disability scale scores.

			Slowed conduction velocities (-)		Slowed conduction velocities (+)		p-value	
Age		Mean±SD (Median)	52±18.2	57.5	51.1±19	53	0.816	^m
Gender	Female	n-%	15	41.7%	13	41.9%	0.982	^{x²}
	Male	n-%	21	58.3%	18	58.1%		
CSF protein		Mean±SD (Median)	112.1±71.2	88.3	110.7±66.8	103.1	0.995	^m
HDS score on the first day		Mean±SD (Median)	2.7±1.1	3	3.1±1.1	3	0.173	^m
HDS score at the first month		Mean±SD (Median)	1.6±1.2	1.5	2.0±1.1	2	0.054	^m
First day – First month change		Mean±SD (Median)	-1.1±1.2	-1	-1.1±0.7	-1	0.256	^m
HDS intragroup change p			<0.01 ^w		<0.01 ^w			
			Abnormal F-waves (-)		Abnormal F-waves (+)		p-value	
Age		Mean±SD (Median)	49.8±18.3	53	52.5±18.6	59	0.575	^m
Gender	Female	n-%	8	36.4%	20	44.4%	0.529	^{x²}
	Male	n-%	14	63.6%	25	55.6%		
CSF protein		Mean±SD (Median)	105.9±69	77.8	114.1±69.1	102.1	0.669	^m
HDS score on the first day		Mean±SD (Median)	2.6±1.1	2.5	3.0±1.1	3	0.12	^m
HDS score at the first month		Mean±SD (Median)	1.3±0.8	1	2.0±1.2	2	0.011	^m
First day – First month change		Mean±SD (Median)	-1.3±0.6	-1	-1.0±1.1	-1	0.326	^m
HDS intragroup change p			<0.01 ^w		<0.01 ^w			
			Prolonged distal latencies (-)		Prolonged distal latencies (+)		p-value	
Age		Mean±SD (Median)	51.3±18.1	57.5	51.8±18.9	54	0.98	^m
Gender	Female	n-%	12	42.9%	16	41%	0.881	^{x²}
	Male	n-%	16	57.1%	23	59%		
CSF protein		Mean±SD (Median)	98.1±65.8	72	121.0±69.9	115.9	0.145	^m
HDS score on the first day		Mean±SD (Median)	2.7±1.2	3	3.1±1.1	3	0.241	^m
HDS score at the first month		Mean±SD (Median)	1.6±1.3	1.5	1.9±1	2	0.084	^m
First day – First month change		Mean±SD (Median)	-1.1±1.4	-1	-1.1±0.6	-1	0.335	^m
HDS intragroup change p			<0.01 ^w		<0.01 ^w			
			Conduction block (-)		Conduction block (+)		p-value	
Age		Mean±SD (Median)	51.1±17.8	54	52.1±19.3	61	0.90	^m
Gender	Female	n-%	11	32.4%	17	51.5%	0.112	^{x²}
	Male	n-%	23	67.6%	16	48.5%		

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Table 2. Continuation.

		Conduction block (-)		Conduction block (+)		p-value	
CSF protein	Mean±SD (Median)	102.5±72	64.4	120.6±64.8	110	0.124	^m
HDS score on the first day	Mean±SD (Median)	2.7±1.2	3	3.1±1	3	0.077	^m
HDS score at the first month	Mean±SD (Median)	1.6±1.3	2	2.0±0.9	2	0.112	^m
First day – First month change	Mean±SD (Median)	-1.1±1.3	-1	-1.2±0.7	-	0.871	^m
HDS intragroup change p		<0.01 ^w		<0.01 ^w			

^m: Mann-Whitney's U test; ^w: Wilcoxon's test; ^{x²}: chi-square test; CSF: cerebrospinal fluid; HDS: Hughes disability scale; SD: standard deviation.

Table 3. Correlation analysis of patients divided into three groups.

		None		One criteria		Two or more criteria		p-value	
		Mean±SD/n-%	Median	Mean±SD/n-%	Median	Mean±SD/n-%	Median		
Age		51.5±18.5	53	55.5±16.2	61	50.2±19.4	53	0.655	^k
Gender	Female	5	38.5%	6	40%	17	43.6%	0.937	^{x²}
	Male	8	61.5%	9	60%	22	56.4%		
CSF protein		110.8±64.6	87.6	92.8±73.5	67.9	118.8±68.4	103.5	0.323	^k
HDS score on the first day		2.5±1.1	2	2.7±1.3	3	3.1±1	3	0.242	^k
HDS score at the first month		1.2±0.8	1	1.9±1.5	2	1.9±1	2	0.058	^k
First day – First month change		-1.4±0.7	-1	-0.8±1.7	-1	-1.1±0.7	-1	0.646	^k
HDS intragroup change p		<0.01 ^w	<0.01 ^w			<0.01 ^w			

^k: Kruskal-Wallis; ^w: Wilcoxon test; ^{x²}: chi-square test; CSF: cerebrospinal fluid; HDS: Hughes disability scale; SD: standard deviation.

Table 4. Correlation analysis of disability scores, cerebrospinal fluid protein levels, and number of demyelinating criteria.

		CSF protein	HDS score 1st day	HDS score 1st month	HDS intra group change
Number of criteria	r	0.139	0.241	0.318	0.121
	p	0.264	0.049	0.009	0.33
CSF protein	r		0.334	0.292	-0.182
	p		0.006	0.016	0.14

Spearman's correlation.

CSF: cerebrospinal fluid; HDS: Hughes disability scale.

antibodies, which are markers for nervous system inflammation⁷. Approximately 50% of GBS patients may show elevated levels in the first week, and this ratio may rise to 80% in the second week⁶. In our study, lumbar puncture was performed at the end of the first day. Higher CSF protein levels have been reported to show a significant loss of the blood brain barrier integrity²¹. Prognostic implications of CSF protein levels for disease activity have been shown in previous studies^{6,15,22}. Our study was compatible with previous studies, and we found that higher CSF protein levels were correlated with worse prognosis on both the first day and first

month. CSF protein levels did not correlate with the number of electrophysiologic abnormalities or any single specific criterion. This can be attributed to the early evaluation of these parameters. DiCapua et al. performed a study with a smaller patient group and demonstrated that the degree of CSF protein elevation correlated with the number of electrophysiologic abnormalities on NCS, but not with any single specific criterion in patients with GBS⁶. Future studies may be beneficial if the patients can be followed using serial lumbar punctures and NCS. It is expected that if this were done, the proportion of Cornblath demyelination criteria that were met would increase and the CSF protein levels would rise, providing valuable information that could be used to finalize a prognosis.

GBS patients are often evaluated with electrophysiological studies within seven days after the symptom onset in the clinical practice. However, there is no current scientific rationale regarding the optimal timing of these studies. For the diagnosis of AIDP, electrophysiological findings are required to be markedly suggestive of demyelination. They include the presence of slowed conduction velocities, prolonged distal latencies, abnormal F-waves in at least three nerves, temporal dispersion, and/or complete or partial conduction block¹⁸.

However, only 80% of the patients fulfilled at least one of the demyelinating criteria. Abnormal F-waves and prolonged distal latencies were the most frequent abnormalities in our study. Previous studies have conflicting results. A study performed with 38 patients in the first 24 hours has shown that the most frequent abnormality was abnormal F-waves⁶. In another study, patients were evaluated in the first seven days and the most frequent abnormalities were reported as prolonged distal latencies and slowed conduction velocities²³. In a study carried out by Gordon et al.²⁴, abnormal F-waves were detected in 25 patients (84%), which was the second most frequent abnormality after the H reflex. Our study was consistent with the work done in prior studies by other authors, but it seems that the timing of the electrophysiological tests is critical in determining the sensitivity of these criteria.

The prognostic value of electrophysiologic findings was evaluated in a small number of studies^{13,14,15,20,24}. The potential amplitude of reduced compound muscle action was the most consistent electrophysiological finding predictive of poor outcome in a previous study¹³, but that was not confirmed by Soysal et al.²⁵. Most of the prior literature works compared axonal and demyelinating features. Our study demonstrates that as the number of demyelinating criteria increases in AIDP patients, a worse prognosis is found on the first day and first month. However, the HDS scores did not correlate

with any single specific criterion. That might be due to the division of the patients into four subgroups. Otherwise, this correlation is demonstrated when the electrophysiological measurements are completed within 24 hours, and one can argue that if the patients could be followed with serial NCS, a higher proportion of these criteria would be satisfied.

Nevertheless, the study has some limitations. It has a retrospective design and NCS were conducted by different practitioners. But the same author evaluated all of the records. CSF analysis and NCS were only assessed at the end of the first day, and the data of the later disease phases were not evaluated. The A waves and H reflexes, which are early potential markers of GBS were not explored. We used old electrophysiological criteria that have relatively low sensitivity for diagnosis. The new diagnostic criteria could enable more accurate diagnoses. Finally, there was a lack of serological studies for anti-ganglioside antibodies, and there was no follow-up after the first month.

Altogether, our study presents the role of the demyelinating criteria and CSF protein levels as prognostic markers of outcome in AIDP. This paper provides the most extensive electrophysiological data reported in early AIDP. In our opinion, more systematic studies conducted with serial NCS are required to highlight the roles of suggested criteria in the clinical practice.

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