

Correlation of Total Protein in Cerebrospinal Fluid with the Type of Guillain-Barre Syndrome based on the Electrodiagnostic Examination at Prof. Dr. IGNG Ngoerah General Hospital Denpasar

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ABSTRACT

Introduction: Guillain-Barre syndrome (GBS) is an autoimmune disease of the peripheral nervous system with an incidence of around 0.6 to 2.4 cases per 100,000 population. GBS pathogenesis is related to inflammatory factors, cytokines, chemokines, and complement. Protein levels in the cerebrospinal fluid of GBS patients will increase due to damage or increased permeability of the blood-nerve barrier and blood-cerebrospinal fluid (CSF) barrier. However, there are still pros and cons to the relationship between the amount of CSF protein and the subtype of GBS.

Objective: To determine the most common GBS subtype and the characteristics of electrodiagnostic examination at Prof Dr IGNG Ngoerah General Hospital and the relationship between the GBS subtype characteristics on electrodiagnostic examination and CSF protein levels.

Methods: This study used an analytic observational study with a cross-sectional study design with consecutive sampling. The sample of this study is 42 GBS patients (21 patients with normal total protein and 21 patients with increased total protein) at Prof Dr IGNG Ngoerah General Hospital, Denpasar-Bali. Data is collected through medical records and analyzed by Chi-Square test.

Results: There is no correlation between the increase in total CSF protein in GBS patients and the GBS subtype on electrodiagnostic examination ($p=0.215$).

Discussion: The most common GBS subtype is the AIDP type. Although the average amount of CSF protein was higher in the AIDP, AMAN and AMSAN subtypes respectively, the increase in total CSF protein did not have a significant relationship to the GBS subtype in Prof Dr IGNG Ngoerah General Hospital, Denpasar-Bali.

Keywords: Guillain-Barre syndrome, autoimmune, total protein, cerebrospinal fluid, AIDP, AMAN, AMSAN

INTRODUCTION

Guillain-Barre syndrome (GBS) is an autoimmune disease of the peripheral nervous system with characteristics of progressive symmetrical ascending flaccid weakness of the extremities accompanied by hyporeflexia or areflexia, mostly preceded by infection. Approximately one third of cases of GBS are preceded by a respiratory or gastrointestinal infection with *Clostridium tetani*. (Yadegari, Nafissi and Kazemi, 2014; Dicapua et al., 2015; Wang et al., 2015; Altaweel et al., 2018; Li et al., 2018; Yang, Lu and Bao, 2018; Péter et al., 2020; Tunç et al., 2020) The incidence of GBS is around 0.6 to 2.4 cases per 100,000 population. Inflammatory factors and cytokines, chemokines, complement play an important role in the pathogenesis of GBS. The outer wall of *C. jejuni* is in the form of

a lipooligosaccharide that resembles a ganglioside causing an autoantibody reaction with a mechanism called molecular mimicry. (Dicapua et al., 2015; Wang et al., 2015; Huang et al., 2018; Yang, Lu and Bao, 2018; Hashim, Mohamed and Emad, 2020) Electrodiagnostic examination also plays an important role in diagnosing GBS apart from clinical manifestations and laboratory results. Electrodiagnostic examination is also important in differentiating motor neuron disease and myopathy. (Gonzalez-Quevedo et al., 2009; Yadegari, Nafissi and Kazemi, 2014; Dicapua et al., 2015)

Electrodiagnostic examinations can distinguish the subtypes of GBS, namely the demyelinating type and the axonal type. The demyelinating type is also known as acute inflammatory demyelinating polyneuropathy (AIDP), in which the immune response damages the myelin sheath causing disruption of nerve impulse transmission, while the axonal type is divided into 2 types: those that only cause motor disturbances called acute motor axonal neuropathy (AMAN) and those that affecting motor and sensory is called acute motor sensory axonal neuropathy (AMSAN). In addition, electrodiagnostic examination can also estimate the prognosis and degree of damage. (Olshansky, 2007; Fokke et al., 2014; Yadegari, Nafissi and Kazemi, 2014; Nomani et al., 2015; Wang et al., 2015; Altaweel et al., 2018)

Protein levels in the cerebrospinal fluid of GBS patients will increase due to damage or increased permeability of the blood-nerve barrier and blood-cerebrospinal fluid barrier with 80% coming from the blood and 20% coming from the brain. (Gonzalez-Quevedo et al., 2009; Dicapua et al., 2015; Wang et al., 2015). CSF protein levels are usually normal in the first week of onset, and will increase in the 2nd and 3rd week of onset. In the studies conducted, there are still pros and cons regarding the relationship between the amount of protein in the CSF and the subtype of GBS. The study conducted by Pei et al., stated that there was no significant difference between the amount of protein

expression between AIDP and AMSAN subtypes. (Nomani et al., 2015; Li et al., 2018) Therefore, the aim of this study was to determine the subtype GBS and the characteristics of the electrodiagnostic examination that most often occur in Prof Dr IGNG Ngoerah General Hospital with the relationship between the characteristics of the GBS subtype on electrodiagnostic examination and protein levels in the cerebrospinal fluid.

RESEARCH METHODS

Research design

This study used an analytic observational study with a cross-sectional research design. This study was conducted by collecting data from medical records of all patients at Prof Dr IGNG Ngoerah General Hospital, Denpasar Bali from January 2016 to December 2020 who were diagnosed with Guillain Barre syndrome based on National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) criteria with an onset of no more than 2 weeks and both electrodiagnostic examination and lumbar puncture has been carried out. This study does not require consent from the patient because it is a retrospective study.

The data collected is secondary data contained in the medical record, including the patient's identity, the results of the electrodiagnostic examination, and the total protein value in the cerebrospinal fluid in the patient. This study was conducted to assess the relationship between total protein in the cerebrospinal fluid and the subtype of GBS in patients based on the results of electrodiagnostic examinations.

Electrodiagnostic examination using electrodes and stimulators including assessing nerve conduction velocity and electromyography using a machine from NATUS. The temperature in each extremity is kept above 32°C. Nerve conduction velocity examination was performed on at least four motor nerves such as the median, ulnar, tibial and peroneal nerves and three sensory nerves such as the median, ulnar

and sural nerves according to the Gordon and Willbourn protocol. In the motor nerves, the values of amplitude (CMAP, distal latency, and nerve conduction velocity) were collected, and in the sensory nerves, the values of latency, nerve conduction velocity and amplitude (SNAP) were also collected. Demyelination and axonal subtypes were distinguished according to the criteria of Ho and Hadden et al., and the AMSAN subtypes were differentiated according to the criteria of Rees et al.

Lumbar puncture for examination of cerebrospinal fluid was carried out in a lateral decubitus position with a normal total protein value in our laboratory below 45 mg/dL.

Research Inclusion and Exclusion Criteria

The inclusion criteria for this study were patients diagnosed with GBS at Prof Dr IGNG Ngoerah General Hospital, Denpasar-Bali and having had a lumbar puncture (total protein value) and complete electrodiagnostics. Exclusion criteria for this study were patients diagnosed with GBS but did not have complete data in the medical record, had other infectious diseases assessed by the presence of sepsis or other foci of infection, had a history of blood disorders, kidney problems, history of allergies, or liver problems.

Place and time of research

The research was carried out at Prof Dr IGNG Ngoerah General Hospital, Denpasar-Bali on May 1st 2021 until the number of samples was fulfilled.

Research variable

The variables in this study were total protein in cerebrospinal fluid and GBS subtype based on electrodiagnostic examination.

Research Data Processing

From the research data (Figure 1), was analyzed statistically. The research data were collected and entered into a computer using *Microsoft Excel* and processed using the *SPSS 24 for windows* program with the research variables being total protein in cerebrospinal fluid and GBS subtypes based on electrodiagnostic examination. Univariate analysis then will be carried out to determine the frequency of each variable. In this study, the relationship between total protein in cerebrospinal fluid and GBS subtype based on electrodiagnostic examination was analyzed using the Chi-Square test. The requirements for testing with the Chi-Square test are cells that have an expected value of less than five, a maximum of 20% of the number of cells and a 2x2 table. The level of significance is expressed as $p < 0.05$ with a 95% confidence interval.

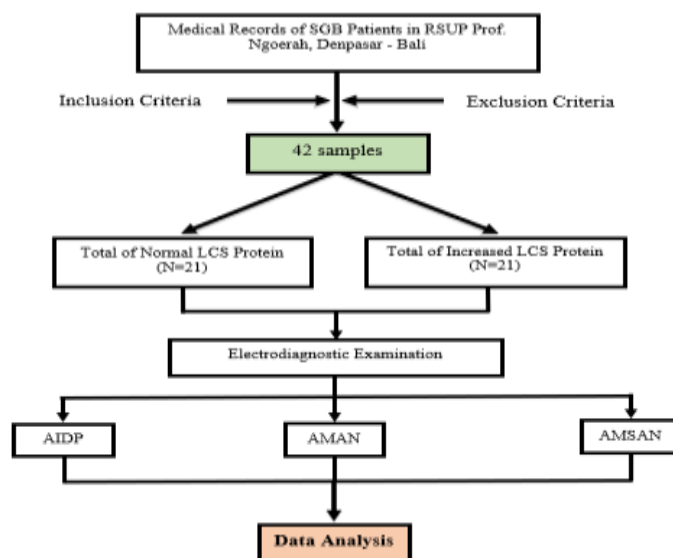


Figure 1. Data Retrieval Flow

RESEARCH RESULTS

Based on research data that has been collected from Guillain-Barre syndrome patients treated at Prof Dr IGNG Ngoerah General Hospital, Denpasar-Bali, 42 patients met the inclusion and exclusion criteria in the study. The researchers divided the study sample into 2 groups, which is the group with lumbar puncture laboratory results showing normal CSF total protein and the group with increased CSF total protein with the number of patients in each group being 21 patients.

Table 1. Characteristics of Guillain-Barre Syndrome Patients

Patients' Characteristics		
Characteristics	Frequency (N=42) (%)	Mean ± SD
Age (Years)		23.33 ± 16.87
Gender		
Male	20 (47.6)	
Female	22 (52.4)	
Total CSF Protein		
Normal	21 (50)	
Increased	21 (50)	
GBS Type		
AIDP	23 (54.8)	
AMAN	8 (19.0)	
AMSAN	11 (26.2)	

The data in Table 1 shows that men and women with GBS sufferers are almost the same with a dominance of women, namely 52.4% (N = 22) with an average age of GBS sufferers of 23.33 ± 16.87 years. Based on the research, it was found that the GBS

subtypes were obtained from the electrodiagnostic examination results, namely AIDP, AMAN and AMSAN with a dominance of the demyelination type, namely AIDP with a percentage of 54.8% (N=23). The results of a more complete examination of nerve conduction velocities, both motor and sensory, can be seen in Tables 3 and 4.

The age predilection for the AIDP and AMSAN subtypes is 40 years, while the AMAN subtype has a younger age of 20 years (Figure 2). The mean amount of CSF protein was higher in the AIDP, AMAN and AMSAN subtypes respectively (Table 2).

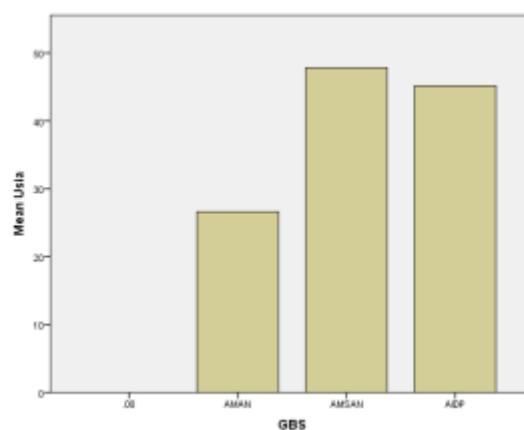


Figure 2. Comparison of Average Age by GBS Subtype

Table 2. Characteristics of Patients Based on Guillain Barre Syndrome Type

Patients' Characteristics	AIDP (n= 23)	AMAN (n=8)	AMSAN (n=11)
Age, Average (min-max)	47.17 (17-72)	26.63 (6-47)	47.82 (22-77)
Gender (Male/Female)	12/ 11	4/4	4/7
Total CSF Protein, average (min-max)	61.29 (15.40-149.20)	50.36 (29-80.60)	43.02 (20.30-66.18)

Table 3. Overview of Motor Nerve Electrodiagnostic Examination Based on GBS Subtypes

Nervus	AIDP	AMAN	AMSAN
Median			
Amplitude (M-mV/S-uV)	4.75 (0-13.20)	2.5 (0.24-5.30)	5.29 (0.47-11.30)
Distal Latency (ms)	7.22 (0-29.20)	3.5 (2.71-4.31)	4.25 (2.85-5.50)
NCV (m/s)	45.46 (0-70.10)	59.5 (44-76.50)	54.10 (38.10-69.80)
Ulnar			
Amplitude (M-mV/S-uV)	4.56 (0.15-9.50)	3.5 (1.89-7.30)	4.08 (0.55-8.10)
Distal Latency (ms)	4.26 (1.56-15.90)	2.6 (1.54-3.60)	2.93 (1.90-3.99)
NCV (m/s)	53.16 (30.90-80.80)	60.6 (43.90-77.20)	62.86 (48.30-80.80)
Peroneal			
Amplitude (M-mV/S-uV)	2.03 (0-5.30)	1.11 (0.26-1.78)	2.18 (0.02-5.20)
Distal Latency (ms)	11.42 (1.83-30)	4.52 (3.11-7.11)	4.70 (3.33-6.15)
NCV (m/s)	33.17 (0-58)	50.24 (37.50-64.70)	41.79 (13.60-58.50)
Tibial			
Amplitude (M-mV/S-uV)	5.51 (0-25)	4.61 (1.07-18.60)	5.64 (0.16-11.20)
Distal Latency (ms)	8.93 (0-35.20)	5.41 (3.79-8.02)	5.96 (3.60-8.24)
NCV (m/s)	62.91 (0-438)	130.31 (36.10-729)	40.65 (8.20-51.60)

Table 4. Overview of Sensory Nerve Electrodiagnostic Examination Based on GBS Subtypes

Nerve	AIDP	AMAN	AMSAN
Median			
Amplitude (M-mV/S-uV)	12.26 (0-37.30)	21.41 (5.90-47.50)	6.26 (0.50-18.90)
Distal Latency (ms)	3.46 (0-7.35)	2.97 (2.31-3.88)	3.13 (1.50-4.06)
NCV (m/s)	41.72 (0-87.50)	60.75 (44-88.80)	56.79 (40.90-127)
Ulnar			
Amplitude (M-mV/S-uV)	14.99 (0.25-66.30)	15.63 (4.10-31.50)	4.45 (1.18-9.20)
Distal Latency (ms)	3.26 (0.37-8.64)	2.55 (2-3.63)	2.82 (1.68-3.76)
NCV (m/s)	76.78 (18.40-571)	62.38 (47-75.90)	56.92 (0-107)
Sural			
Amplitude (M-mV/S-uV)	12.35 (0.25-92.30)	28.13 (3.70-164)	4.81 (0-18.50)
Distal Latency (ms)	4.85 (1.11-15.20)	3.19 (1.05-4.07)	3.51 (0-5.50)
NCV (m/s)	50.98 (9.40-200)	53.58 (43.20-87)	45.34 (0-72.20)

Based on the analysis using Chi-square, there was no significant difference between the increase in total CSF protein to the GBS

subtype based on the results of electrodiagnostic examination with a p value <0.05 (Table 5).

Table 5. Relationship Between Total CSF Protein in GBS Subtypes

		GBS Subtypes				N	p value*
		Axonal		Demyelination			
		n	%	n	%		
Normal CSF Protein	Count	12.0	57.1%	9.0	42.9%	21	0.215
	Expected Count	9.5		11.5			
Increased CSF Protein	Count	7.0	33.3%	14.0	66.7%	21	
	Expected Count	9.5		11.5			
Total	Count	19.0	45.2%	23.0	54.8%	42	
	Expected Count	19.0		23.0			

DISCUSSION

Guillain-Barre syndrome is an autoimmune disease with a fatality rate of 5% to 10% with various clinical manifestations. (Hashim, Mohamed and Emad, 2020) The prognosis for GBS depends on the patient's onset at admission to the hospital and the time of treatment of the patient. In addition, the prognosis is also affected by GBS subtypes, therefore by differentiating GBS subtypes we can help in determining the prognosis of patients. (Nomani et al., 2015) Patients over 40 years of age, high total CSF protein, history of previous gastrointestinal disease, poor clinical manifestations, axonal subtype on electrodiagnostic examination, and increased need for a ventilator are factors for a worse prognosis in patients with GBS. (Nomani et al., 2015)

The results of this research showed that GBS patients were almost the same between men and women with a dominance of women, namely 52.4% (N=22). This is different from several studies conducted such as the study conducted by Fokke et al., Sejvar et al., Nomani et al., where sex predilection was more common in men. However, in a study conducted by

Gonzalez-Suarez and et al., there was no significant difference in gender for the incidence of GBS. (Nomani et al., 2015; Altaweel et al., 2018) Some studies suggest that GBS can occur at any age. In this study, the mean age of GBS patients was 23.33 ± 16.87 years. In the study conducted by Nomani et al., the mean age of GBS was 34.7 ± 18 years. The most common subtype is the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) subtype. AIDP is more common in Caucasians, whereas axonal subtypes such as AMAN and AMSAN are more common in Chinese and Pakistani populations. This is consistent with the results of our study, namely the dominance of the demyelinating type, namely AIDP, with a percentage of 54.8% (N=23). (Olshansky, 2007; Fokke et al., 2014; Dicapua et al., 2015; Nomani et al., 2015; Sevki Sahin, Nilgun Cinar, 2017; Yang, Lu and Bao, 2018)

In a study conducted by Bourque et al., it was found that an increase in total protein in the cerebrospinal fluid correlated with the GBS subtype, with the AMAN subtype having the lowest total protein compared to the AMSAN and AIDP subtypes. In

addition, there is an up to two-fold increase in the total protein in the cerebrospinal fluid in the demyelinating subtype compared to the axonal subtype. This is consistent with mechanisms such as damage to the myelin sheath resulting in the release of myelin protein from spinal axon fibers, and more obvious damage to the blood-nerve barrier in spinal fibers. (Bourque et al., 2020) Increased total protein in cerebrospinal fluid correlates with prognosis the worse include abnormalities from electrodiagnostic examinations. (Tunç et al., 2020)

An increase in total CSF protein indicates an increase in antibodies and myelin damage. The increase in total protein in CSF that occurs in the first week of onset is associated with an increase in the severity of GBS disease caused by swelling of the spinal roots resulting in disruption of CSF reabsorption. This occurs due to protein accumulation in the arachnoid villi caused by inflammation of the dorsal and ventral roots. This total protein is thought to be a marker and associated with damage and progression of demyelinating disease. (Gonzalez-Quevedo et al., 2009; Sevki Sahin, Nilgun Cinar, 2017)

Increased total protein in the cerebrospinal fluid plays a role in the pathophysiology of the GBS subtype, which is a marker of extension to the radicular, the degree of damage to the blood-nerve barrier, and damage to myelin or binding of antibodies to axons. (Bourque et al., 2020) In the early stages, leukocytes will invade peripheral nervous system, causing demyelination. The damaged blood-nerve barrier will be crossed by T-cells and cause a local inflammatory response. Damage to the blood-nerve barrier causes an increase in immunoglobulins in the spinal roots and is associated with neurological deficits. (Gonzalez-Quevedo et al., 2009) The AIDP subtype has a higher total CSF protein based on the findings of a study by Yadegari et al. (Yadegari, Nafissi and Kazemi, 2014; Nomani et al., 2015) However, an increase in the total protein in the cerebrospinal fluid was also found to have no significant value for the subtype of

GBS, namely in a study conducted by Rath, et al., where the amount of protein in the cerebrospinal fluid did not differ in SGB subtype with a value of $p=0.054$. However, based on numerical data, the pure motor subtype has a lower amount of CSF protein than the sensorimotor subtype. (Rath et al., 2021) In addition, a high total CSF protein is often associated with a higher degree of damage and a worse prognosis for GBS sufferers, so High total protein has an indirect relationship with axonal subtype rather than demyelinating subtype. (Nomani et al., 2015).

However, based on data analysis, our results did not show a significant difference between increases in total CSF protein to GBS subtypes (Table 5).

The limitations of this study are the non-specific onset of electrodiagnostic examination and lumbar puncture in patients, and also the examination of total protein in cerebrospinal fluid which is less specific as a marker of damage to the blood-nerve barrier. Therefore, it is recommended that other more specific laboratory tests can be carried out for future studies.

CONCLUSION

Based on the results of research conducted, the most common subtype of Guillain-Barre Syndrome in patients treated at Prof Dr IGNG Ngoerah General Hospital, Denpasar-Bali, is the AIDP type. Although the average amount of CSF protein was higher in the AIDP, AMAN and AMSAN subtypes respectively, after analyzing the data, no significant results were obtained. The increase in total protein in cerebrospinal fluid did not have a significant relationship to the guillain-barre syndrome subtype from the results of electrodiagnostic examinations conducted at Prof Dr IGNG Ngoerah General Hospital, Denpasar-Bali.

Declaration by Authors

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