Original Article

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CSF Neurofilament-H Levels as a Potential Prognostic Marker in Patients of Guillain-Barré Syndrome- A Cohort Study

Internal Medicine Section

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ABSTRACT

Introduction: The prognosis of Guillain-Barré Syndrome (GBS) at an early stage with explicit biomarkers is critical to distinguish patients with possibility of poor recovery. Cerebrospinal Fluid (CSF) serves as an impending source for biomarkers that portrays the exact biochemical changes.

Aim: To find out if there is any prognostic value of high CSF phosphorylated Neurofilament Heavy subunit (pNf-H) levels, measured during first two weeks of onset of GBS, as assessed by the level of disability at six months after the onset of GBS.

Materials and Methods: The cohort study was conducted in the Department of Neurology and Department of Immunology and Molecular Medicine, at the Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India, over a period of two years from August 2015 to August 2017. Sixty two patients who satisfied the required diagnostic standards for GBS (study group) and 35 patients with tension-type headache (control group) were selected for the study. After clinical and electrophysiological assessment, CSF samples were collected. A commercially available sandwich enzyme immunoassay kit, manufactured by BioVendor-Laboratorní medicína (Czech Republic), was used for measuring human pNf-H quantitatively.

Results: Mean CSF pNf-H level in patients with good outcome was 325.3 pg/mL whereas, in patients with poor outcome it was 3655.2 pg/mL. CSF pNf-H levels were found to be suggestively higher in GBS patients with poor outcome as compared to those with good outcome. Only eight patients in good outcome group had pathologically high CSF Nf-H levels whereas 10 patients in poor outcome group had CSF Nf-H levels ≤730 pg/mL. The odds ratio was 17.1 (95% Confidence Interval (CI) 3.83-76.29). Thus, high CSF Nf-H levels on admission predicted poor outcome in GBS (p-value <0.001). Moderate degree of positive correlation was found between CSF Nf-H levels and outcome (F score) at six months (R=0.684; p-value <0.001).

Conclusion: It can be determined that higher values of CSF pNf-H in GBS (acute stage), could serve as a predictive marker indicative of poor prognosis.

Keywords: Acute motor axonal neuropathy, Axonal degeneration, Biomarker

INTRODUCTION

The GBS is referred to as a disease with a single phase distinguished by acute onset, immune mediated (cellular and humoral) polyradiculoneuropathy that may be axonal or demyelinating. It is clinically characterised as rapidly evolving areflexic weakness and sensory disturbance in the limbs and associated with weakness of facial, bulbar and respiratory muscles [1]. GBS can be categorised into:- Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP), Acute Motor Axonal Neuropathy (AMAN), Acute Motor and Sensory Neuropathy (AMSAN), acute sensory neuronopathy, acute pandysautonomia and Miller Fisher Syndrome (MFS) [2,3]. Studies have reported the incidence of GBS is 0.6-4 cases/100000 across the world [4,5]. GBS is commonly seen to be affecting the males more than the females and its incidence rises with age [6,7].

The microorganisms contributing to the infectious state include: *C jejuni,* Cytomegalovirus (CMV), Epstein Barr virus (EBV), M. pneumonia, H. influenza [8,9]. It is also seen to occur after vaccination, surgery and head injuries [10,11]. GBS is characterised by weakness in the lower extremities bilaterally (most commonly), and sometimes the upper limbs [12,13]. The clinical presentation includes paraparesis, muscular pain, bulbar and ocular nerve involvement, respiratory muscle weakness, dysautonomia, hyporeflexia or areflexia [14,15]. Early prognostication of GBS with specific biomarkers is essential to recognise patients with probability of poor recovery [16,17]. CSF is probably an important spring for biomarkers, whose compartment has close proximity with the nerve roots exhibiting meticulous biochemical changes [18]. The biomarkers associated with the disease include CSF neurofilaments, 14-3-3 protein, complement components C3a and C5a, tau protein, soluble fractalkine, cystatin C and B, chemokines, antibodies against myelin basic protein and anti-GM1 antibodies [19,20]. Elevated levels of CSF neurofilaments (CSF Nf-H) are observed in several neurodegenerative diseases wherein, few studies have assessed the role of CSF Nf-H as an early prognostic marker [21,22].

Hence, the present study was conducted with the aim to find out if there is any prognostic value of high CSF pNf-H levels, measured during first two weeks of onset of GBS, as assessed by the level of disability at six months after the onset of GBS.

MATERIALS AND METHODS

The cohort study was conducted in the Department of Neurology and Department of Immunology and Molecular Medicine, at the Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, over a period of two years from August 2015 to August 2017, with a follow-up period of six months. The study was approved by Hospital Ethical Committee (IEC/SKIMS Protocol RP 08/2018) and written informed consent was obtained from all the participants.

Sample size calculation: Using GPower software, it was estimated that a minimum of 90 subjects with 60 cases and 30 controls were needed to be included in present study with 80% power, 5% significance level and an allocation ratio of 2:1.

Inclusion criteria:

- Sixty two participants who fulfilled the diagnostic criteria for GBS, (as compiled by Asbury and Cornblath criteria), with areflexia and progressive motor weakness of more than one

limb and those who reported in the first two weeks of the disease onset were included in the study [1].

- MFS, which is not covered by this criteria was diagnosed as a triad of acute onset of ophthalmoplegia, areflexia and ataxia after ruling out other aetiologies [23].
- Patients with past history of GBS, who presented with fresh episode were also included in the study.
- Thirty five patients with tension-type headache with no neurological pathology and who had normal CSF findings, matched for age and gender, were included in the control group.

Exclusion criteria

- GBS patients presenting after two weeks of onset of symptoms.
- Patients having recent history of traumatic brain injury, spinal cord injury, subarachnoid haemorrhage or stroke.
- Patient suspected with underlying condition that alter Nf-H levels in CSF (e.g., Amyotrophic lateral sclerosis, Alzheimer's disease, Parkinsons disease, etc.).

Clinical Evaluation and Study Protocol

The demographic and clinical data were collected including age, sex, first neurological symptom to present and presence of any previous disease with respect to respiratory tract infection, diarrhoea and influenza like illness. CSF was examined for microscopic and biochemical parameters including total cell count, protein and sugar.

Data regarding day of illness on which patient was admitted, season of presentation (Winter, Spring, Summer, Autumn), duration between preceding illness and onset of symptoms, duration of hospital stay, need for ventilatory support, growth of autonomic dysfunction and time duration to acquire ultimate shortfall were recorded. A thorough motor system assessment was performed comprising of cranial nerve examination, power and reflexes. Complete Blood Count (CBC), blood sugar and biochemical parameters including RFT and LFT were done in all patients as general routing investigative procedures. All patients underwent electrophysiological assessment on admission using Medelec Synergy equipment (Oxford Instruments Medical, UK). Motor nerve conduction evaluation was conducted by exciting the common peroneal nerve, posterior tibial nerve, median and ulnar nerves to examine compound muscle action potentials comprising onset latency, amplitude and conduction velocity. Sensory nerve conduction assessment was performed to measure sural, median and ulnar sensory nerve action potentials. Mean F wave latency was also measured. Albers JW and Kelly JJ had proposed certain criteria for both demyelinating and axonal varieties for the electrophysiological diagnosis of GBS [24]. To keep the paper focused on the primary objectives, these data have not been included in this article.

Outcome measure: Hughes functional grading scale to assess the general functioning was used as follows:- 0 (normal health), 1 (minor neurological symptoms or signs, being able to run), 2 (able to walk at least 5 m, but unable to run), 3 (able to walk 5 m with walker or support), 4 (bedridden), 5 (ventilated), to 6 (dead) [25]. The F-score was documented at nadir and final follow-up (six months). Outcome was categorized as "poor" (F-score ≥3) if patients were unable to walk independently and "good" (F-score <3) if patients were able to walk independently at follow-up [26].

Sample collection and storage: Quincke lumbar needle (22 or 24 gauge) was used to collect the CSF samples through lumbar puncture with the mean time of about 8.9 days (median eight days). The CSF samples were collected in polypropylene tubes, centrifuged, and stored at -80°C within two hours of sampling in 1.5-2 mL Eppendorf tubes until analysis. All tubes were coded, and CSF was analysed blinded to all other information.

Measurement of CSF phosphorylated neurofilament: A commercially available sandwich enzyme immunoassay kit, manufactured by BioVendor-Laboratorní medicína (Czech Republic), was used for the quantitative measurement of human pNf-H.

STATISTICAL ANALYSIS

The standard curve was constructed by plotting the mean absorbance (Y) of standards against the known concentration (X) of standards in logarithmic scale, using the four-parameter algorithm. The measured concentration of samples calculated from the standard curve was multiplied by their respective dilution factor. Continuous variables were summarised as mean±SD (Standard Deviation) and categorical variables were expressed as frequencies and percentages. Graphically the data was presented using scatter plot. Chi-square test or Fisher's exact test, whichever appropriate, was employed to compare categorical variables. Univariate analysis was used for testing factors potentially associated with outcome. Factors significantly associated with outcome were further tested by logistic regression analysis. Pearson Correlation was used to determine relationship of neurofilament H levels with outcome (F-score). A p-value <0.05 was considered statistically significant. All p-values were two tailed. The recorded data was compiled and final data was exported to data editor of Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

The present study consisted of total 97 adults, 62 subjects were in the study group with GBS and 35 in control group comprising of non GBS headache.

The age distribution, presenting symptom, antecedent illness and CSF cell variation in the study group are given in [Table/Fig-1]. The age of the patients ranged from 18-72 years with a mean age of 44.7 years. Out of 62 cases, 35 were males and 27 were females, the sex ratio being 1.3:1. The predominant initial symptom was lower limb weakness seen in 41 (66.1%) patients followed by sensory symptoms in 9 (14.5%) patients, 1 (1.6%) patient was admitted as a case of MFS who presented with diplopia. Respiratory tract illness (19.4%) was the most common preceding illness. 80.6% patients in present study had CSF cell count less than 5 and none of the patients had more than 50 cells/μL in CSF.

In study group, 4 (6.5%) patients died during the follow-up period due to various causes in and outside the hospital. Out of them three died during hospital stay and were on ventilator support. Two of them died as a result of hospital acquired pneumonia and sepsis. One patient died of myocardial infarction. Two of these patients died on 12th day of illness. The third patient died on 84th day of admission. He was on ventilator support for third day of start of illness and had presented as hyperacute GBS. One 55-year-old male patient who was discharged after nine days of hospital stay died four months after discharge. He was bedridden at home (F-score 4) and had developed bed sores. The exact cause of death in that patient was not known. All the four patients who died had CSF Nf-H levels greater than 730 pg/mL. On electrophysiological study two of them had demyelinating and two had axonal type GBS. In present study 49 (79%) patients had a good outcome, whereas 13 (21%) patients had a poor outcome at six months follow-up [Table/Fig-2]. A statistically significant association was observed between F-score at peak of weakness in hospital and the functional outcome (F-score) at six months follow-up.

The mean CSF Nf-H levels in control patients was 218.6 pg/mL when compared to 1023.54 pg/mL in the study group and the maximum value was 587.6 pg/mL. The population-based upper limit of normal is <730 pg/mL and has been determined using a reference population of 416 patients with a median age of 41.9 (interquartile range, IQR, 31.2-55.8) years [27]. As none of the patients in present control group also had CSF Nf-H levels more than 730 pg/mL, any value above 730 pg/mL was taken as pathological. There was significant difference between mean CSF Nf-H levels between case and control group with p-value 0.025 [Table/Fig-3].

Variables	Frequency	Percentage
Age (years)		
15-24	7	11.4
25-34	11	17.7
35-44	13	21
45-54	10	16.1
55-64	11	17.7
≥ 65	10	16.1
Total	62	100
Symptom		
Lower limb weakness	41	66.1
Upper limb weakness	4	6.5
Weakness all limbs	7	11.3
Sensory symptoms	9	14.5
Diplopia	1	1.6
Total	62	100
Antecedent Illness		
RTI	12	19.4
Diarrhoea	7	11.3
Influenza like illness	6	9.7
Total	25	40.4
CSF Cells		
<5	50	80.6
5-10	7	11.3
11-50	5	8.1
>50	0	0
Total	62	100

[Table/Fig-1]: Age, symptoms, antecedent illness, CSF cell variation in the study group.
RTI: Respiratory tract infection; CSF: Cerebrospinal fluid

F-score	At Nadir		After six months	
	No.	%	No.	%
0	0	0	41	66.1
1	0	0	6	9.7
2	2	3.2	2	3.2
3	17	27.4	6	9.7
4	31	50	3	4.8
5	12	19.3	0	0
6	0	0	4	6.5
Good outcome (0-2)	2	3.2	49	79
Poor outcome (3-6)	60	96.8	13	21

[Table/Fig-2]: Functional Outcome (F-Score) at six months in patients of GBS.
Good outcome at six months: 49 (79%); Poor outcome: 13 (21%)

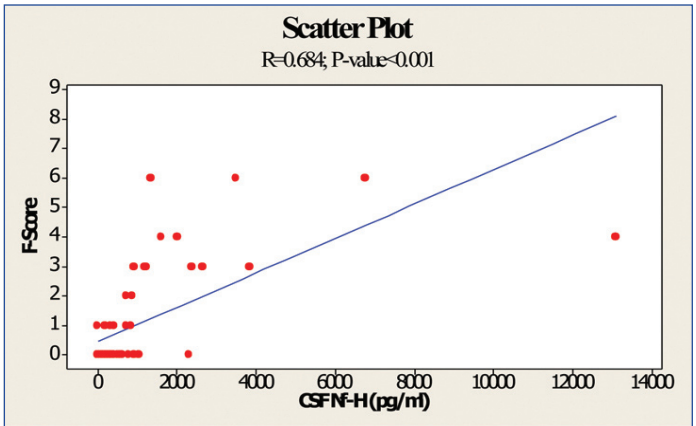
Parameter	Cases		Controls		p-value
	Mean	SD	Mean	SD	
CSF Nf-H levels (mg/dL)	1023.54	2084.5	218.6	108.7	0.025*

[Table/Fig-3]: Comparison of CSF pNf-H levels in cases and controls.
p-value by Students Independent t- test; *statistically significant

As depicted in [Table/Fig-4], the mean CSF pNf-H level in patients with good outcome was 325.3 pg/mL whereas, in patients with poor outcome it was 3655.2 pg/mL. CSF pNf-H levels were significantly higher in GBS patients with poor outcome as compared to those with good outcome using univariate comparisons. Only 8 (16.3) patients in good outcome group had pathologically high CSF Nf-H levels whereas, 10 (76.9%) patients in poor outcome group had CSF Nf-H levels >730 pg/mL. On analysis, the Odds ratio was 17.1 (95% Confidence Interval [CI] 3.83-76.29). Thus, high CSF Nf-H levels predicted poor outcome in GBS (p-value <0.001). Correlation analysis was performed using Pearson's correlation (R). Moderate degree of positive correlation was found between CSF Nf-H levels and outcome (F score) at six months (R=0.684; p-value <0.001). High CSF Nf-H levels were found to correlate with poor outcome [Table/Fig-5].

Parameter	Good outcome 49 patients		Poor outcome 13 patients		p-value
	Mean	SD	Mean	SD	
CSF Nf-H levels (pg/mL)	325.3	413.54	3655.2	3451.1	<0.001*
	No.	%	No.	%	
>730	8	16.3	10	76.9	<0.001*
≤730	41	83.7	3	23.1	

[Table/Fig-4]: Association of CSF pNf-H levels (pg/mL) with outcome (F Score).
p-value by Students Independent t-test and Fischer's exact test. {Odds Ratio (OR) (95% CI) =17.1 (3.83-76.29); *Statistically Significant}



[Table/Fig-5]: Scatter plot showing correlation between CSF Nf-H levels and outcome (F-score).

[Table/Fig-6] and [Table/Fig-7] shows that CSF Nf-H levels are not influenced by age or gender of the patient nor by the timing of performance of lumbar puncture or whether patient had any past episode of GBS. Also, there was no statistically significant correlation between CSF protein levels and CSF Nf-H levels.

Parameter	R value	p-value
Age (years)	0.035	0.785
CSF Protein (mg/dL)	0.159	0.218
Time to lumbar puncture (days)	-0.252	0.058

[Table/Fig-6]: Correlation of CSF pNf-H levels (pg/mL) with age, time to lumbar puncture and CSF protein.
R value=Pearson correlation coefficient; p-value by t-test for significance of observed sample correlation coefficient

Parameter	Male		Female		p-value
	Mean	SD	Mean	SD	
CSF Nf-H levels (mg/dL)	1117.1	2476.0	902.3	1466.4	0.691
	Past episode of GBS		No past episode of GBS		
	Mean	SD	Mean	SD	
	579.3	989.1	296.5	302.6	0.149

[Table/Fig-7]: Comparison of CSF pNf-H levels as per gender and past episode of GBS.
p-value by Student's Independent t-test

DISCUSSION

The GBS being an acute immune-mediated peripheral neuropathy has inconstant clinical consequence that is supposedly recognised by the amount of nerve damage during the acute phase and ability to recover during the convalescent phase [26]. It is however, imperative to identify the outcome and prognosis of the disease state at an early stage which incorporates the use of various biomarkers as has been reported in several studies. By envisaging the prognostic result of the disease accurately, novel drugs like eculizumab etc could be examined in a limited GBS populace having poor prognosis

[12]. It has been reported in earlier studies that diarrhoea (*C. jejuni* infection within four weeks), increased age group (>40 years), fast advancement, nadir disability, and specific electrophysiological features depicted long-term prognosis [28,29].

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological response to therapeutic intervention [30]. The plausible and impending use of biomarkers have been documented in limited studies to elucidate the prognosis of GBS [31]. Serum, CSF and peripheral nerve tissue serve as the chief source of GBS biomarkers amongst which CSF remains the most important one. Proximal nerve roots in the subarachnoid region moving generously in CSF, hence, the transformed protein content of CSF could mimic the damage in the nervous system tissue [18]. The dysfunction of blood-CSF barrier (B-CSF-B) and Blood-Nerve Barrier (BNB) also allows CSF to be essential sources of biomarker [32]. Several studies have been conducted to identify specific biomarkers within the CSF for prognosis and diagnostic of inflammatory neuropathies like GBS, amongst which CSF pNf-H has been assessed as a potent prognostic marker [21,33].

Neurofilaments are obligate heteropolymer, proteins of the neurons and their adjoining axons [34,35]. Axonal degeneration and membrane disintegration leads to the release of the cytoplasmic contents into the Extracellular Fluid (ECF). Neurofilaments diffuse into the fluid compartments like CSF, blood or amniotic fluid from the ECF. The pNf-H are resistant to protease enzymes, hence, pNf-H discharged from disintegrated axons are found un-degraded in the fluid [36,37]. Thus, the recognition of pNf-H in blood and CSF denotes the neuronal damage unequivocally as it is found exclusively in the neurons.

It has been shown in previous studies that an increased level of Nf-H in CSF of GBS patients can be served as a adverse prognostic indicator. Petzold A et al., conducted a prospective study in GBS patients wherein, motor function and disability grades were quantified. They showed that patients with high (>0.73 ng/mL) CSF Nf-H levels were more restricted on both outcome measures at the last follow-up visit [21]. Petzold A et al., in a prospective multicentre study, concluded that high Nf-H levels (>0.73 ng/mL) predicted poor outcome [22]. In a study conducted by Dujmovic I et al., high and increasing levels of CSF Nf-H in serial CSF samples were correlated with poor clinical and electrophysiological outcome [38]. Therefore, these studies suggested that CSF Nf-H could serve to be a prognostic biomarker to indicate retrograde axonal degeneration or any other proximal axonal impairment in GBS.

As mentioned previously, the results of present study were in accordance to studies conducted by Petzold A et al., [21], Petzold A et al., [22] and Lee Y et al., [33] who demonstrated that elevated Nf-H levels in CSF of GBS patients indicated adverse prognosis of the disease. These findings could be justified by the apparent anatomic source for Nf-H. The proximal axonotmesis near the motor nerve root causes release of axonal proteins into the CSF. The identification of the protein biomarkers in the CSF thus, permits the estimation of proximal axonal damage in the acute phase of GBS. Proximal axonotmesis is likely to be more relevant for prognosis than distal axonal damage, because recovery needs axonal regrowth over a long distance along with losing chemical and anatomical guidance signals. In distal axonal damage, detection of biomarkers in CSF sample, shows less prognosis due to axonal sprouting, providing potential for recovery [22].

In India, there are no reported studies that have evaluated prognostic role of CSF Nf-H levels in GBS patients. The biomarker pNf-H levels were measured during the acute stage of GBS and 35 patients were considered as controls who were discharged with the diagnosis of tension type headache. The mean CSF Nf-H levels in the control group was 218.6 pg/mL compared to 1023.54 pg/mL in the study group.

In present study, 49 patients (79%) had a good outcome, whereas 13 patients (21%) had poor outcome at at six months follow-up. This was similar to the results of studies which depicted approximately 20% GBS patients were unable to walk after six months [39,40]. The mean CSF pNf-H level in patients with good outcome in present study was 325.3 pg/mL whereas the mean level in patients with poor outcome was 3655.2 pg/mL. In GBS patients, levels of CSF Nf-H (>730 pg/mL) measured in the sample taken within two weeks of the onset of symptoms prophesied incapability to walk independently at six months (F-score ≥3) with an odds ratio of 17.1 [Table/Fig-4]. Moderate degree of positive correlation was found between CSF Nf-H levels and outcome (F score) at six months (R=0.684; p-value <0.001).

Present study has shown a male:female ratio of 1.3:1, signifying male preponderance, which was similar to few other reported studies [6,7]. Analysis was done to determine any correlation of CSF pNf-H (pg/mL) levels with other variables.

Correlation analysis of CSF pNf-H levels with age, time to lumbar puncture and CSF protein was done and no significant correlation was established. The mean time of lumbar puncture in patients of present study was 8.9 days, so owing to the Ethical Committee restraints, CSF analysis was done only once in these patients. Lumbar puncture was done during second week except in one patient who had presented as hyperacute GBS. Hence, it would be advisable to evaluate CSF Nf-H levels before first week of onset of symptoms so as to correlate with outcome. This would help to prognosticate patients earlier during the course of disease. Six patients in present study had past episode of GBS with complete recovery which had no significant association with CSF pNf-H levels.

The GBS usually follows a monophasic course and does not recur. Kuitwaard K et al. [41] in their study have reported two or more episodes in 7% of patients which had no significant association with poor outcome.

A statistically significant association also exists between F-score at nadir and F-score at six months follow-up. Mean time required to reach peak disability in this study was 8.4 days which was comparable to the studies described by Paul BS et al., [42] and Verma R et al., [43].

Limitation(s)

- A high age has consistently been related to poor prognostic outcome in GBS patients [26,44]. Its lack of association in the present study may be because of small sample size for brevity of paper this data has not been included in the results section.
- The mean time of lumbar puncture in patients of present study was 8.9 days, owing to the Ethical Committee restraints. It would be advisable to evaluate CSF Nf-H levels before first week of onset of symptoms so as to establish its correlation with outcome at earlier stage. This would help to prognosticate patients earlier during the course of disease, at which time early institution of therapy would be beneficial.

CONCLUSION(S)

The present study hence, delivers an indication that high CSF pNf-H levels in acute stage of GBS could serve to be a prognostic marker, with high levels representing a poor prognosis. This is important as GBS patients with suspected poorer prognosis might benefit from more aggressive initial treatment or transfer to specialised centres.

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