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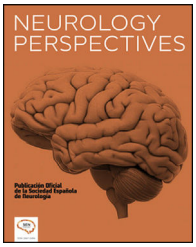

ORIGINAL ARTICLE

Early prognostic factors in acute inflammatory demyelinating polyneuropathy: Role of neurofilaments

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Abstract

Introduction: Guillain-Barré syndrome (GBS) is an autoimmune disease that results in demyelination and axonal damage. Although the recovery is good in most patients, 20% remain significantly disabled.

Neurofilament light chain (NfL) has been established as a biomarker of axonal damage in many diseases.

Methods: We measured NfL, S100B, and glial fibrillary acidic protein (GFAP) concentrations from blood and cerebrospinal fluid (CSF) taken upon admission from 19 patients with a history of GBS between January 2009 and December 2019 and investigated a correlation between them and clinical outcomes.

Results: All patients fulfilled levels 1 or 2 of the Brighton diagnostic.

Preceding infection was reported in 11 cases (58%).

We classified 15 patients as acute inflammatory demyelinating polyneuropathy, 2 as AMAN, 1 as AMSAN, and 2 cases as Miller–Fisher syndrome.

Five patients were transferred to an ICU, with a mean stay of 13 days. Functional outcome at 6 months after discharge was good in 12 patients (70.6%).

We evaluated disease prognosis using the modified Erasmus GBS outcome score. The correlation was significant ($p < .05$) in the case of NfL in serum and CSF and GFAP in CSF ($r = 0.472$ for serum NfL, 0.576 for CSF NfL, and 0.544 for CSF GFAP).

Conclusions: We confirm the finding of elevated levels of NfL, GFAP, and S100B in CSF and plasma in the acute phase of GBS.

We can point out that their value has a certain relationship with the severity of the disease and prognosis, and that in some way, they have an influence, but we would lack more information to make good predictions.

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PALABRAS CLAVE
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Factores pronósticos precoces en AIDP: Papel de los neurofilamentos

Resumen
Introducción: El síndrome de Guillain-Barré (SGB) es una enfermedad autoinmune que provoca desmielinización y daño axonal. Aunque la recuperación es buena en la mayoría de los pacientes, el 20% permanece significativamente discapacitado tras la recuperación. Los factores predictores tempranos aumentarían la probabilidad de identificar a los pacientes con riesgo de mal pronóstico en la fase aguda.

La cadena ligera de neurofilamentos (NfL) se ha establecido como biomarcador del daño axonal en muchas enfermedades del sistema nervioso central.

Métodos: Se midieron las concentraciones de NfL, proteína B fijadora de calcio (S100B) y proteína ácida fibrilar glial (GFAP) en sangre y en LCR de 19 pacientes con diagnóstico de SGB entre enero de 2009 y diciembre de 2019. Posteriormente se intentó establecer una correlación entre éstos y los resultados clínicos.

Resultados: Todos los pacientes cumplían los niveles 1 o 2 de los criterios diagnósticos de Brighton en cuanto a su presentación clínica.

Del total de pacientes con SGB, se registraron infecciones previas en 11 casos (58%), siete con infección digestiva y cuatro con infección respiratoria.

Clasificamos a 15 pacientes como AIDP, dos como AMAN, uno como AMSAN y dos casos como síndrome de Miller-Fisher.

Cinco pacientes fueron trasladados a la UCI, con una estancia media de 13 días. El resultado funcional a los seis meses del alta fue bueno en 12 pacientes (70,6%).

Se evaluó el pronóstico de la enfermedad mediante la puntuación en la escala mEGOS. La correlación fue significativa ($p < 0,05$) en el caso de NfL en suero y LCR y GFAP en LCR ($r = 0,472$ para NfL en suero, 0,576 para NfL en LCR y 0,544 para GFAP en LCR).

Conclusiones: Confirmamos el hallazgo de niveles elevados de NfL, GFAP y S100B en LCR y plasma en la fase aguda del SGB.

Podemos señalar que su valor tiene cierta relación con la gravedad de la enfermedad y el pronóstico, y que de alguna manera influyen, pero nos faltaría más información para hacer buenas predicciones.

Introduction

The Guillain-Barré syndrome (GBS) is a rare condition, but it accounts for the main part of acute flaccid paralysis worldwide. Age-adjusted incidence in Europe has previously been estimated to 1.45–2.30/100.000.[1]

The exact mechanism of GBS remains unknown, but it is currently accepted as an immune-mediated polyradiculoneuropathy resulting from a synergistic interaction between cellular and humoral immune responses to antigens in the peripheral nervous system.

Two-thirds of cases is preceded by bacterial or viral gastroenteritis or respiratory infection.[2] *Campylobacter jejuni*, Epstein–Barr virus, cytomegalovirus, and Zika are the most common infective agents. Recent reports suggested the possible association between acute COVID-19 infection and GBS.[3]

Clinically, GBS is characterized by acute onset and a rapidly progressing ascending type of motor weakness paresthesia which reaches maximum severity within 4 weeks.

The most common variant of GBS in Europe and North America is acute inflammatory demyelinating polyneuropathy (AIDP).[4]

The axonal variant of GBS (AMAN) is caused by axonal degeneration due to aberrant autoimmune responses against peripheral axons.

Patients with evidence of axonal involvement tend to be more severely afflicted by disease and with poorer recovery than patients with demyelinating forms.[5]

Nowadays, the diagnosis is based on clinical history, nerve conduction studies (NCS) and analysis of the cerebrospinal fluid (CSF).

A laboratory hallmark of GBS is the albumin–cytological dissociation in the CSF.

Treatment strategies rely on early diagnosis; plasma exchange (PE) shortens time to neurological improvement, with intravenous immunoglobulin (IVIg) being equivalent.

Predicting disease course, prognosis, and response to immunomodulatory treatment is challenging due to the lack of reliable prognostic biomarkers.[6]

The prognosis in some cases of GBS is rather poor partly attributed to the challenge of identifying these patients early in the presentation and substantial variations in phenotypes.

Currently, 25%–30% of patients require artificial ventilation, 20% remain severely disabled, and the mortality rate is

5% despite immunotherapy and intensive care units (ICUs).[7–10]

The highest efficacy is achieved when treatment starts within 2 weeks from disease onset.

Predictors that identify patients at risk for poor outcome would be desirable in the acute phase.[11–13]

A few outcome scores provide some early prognostic data based on clinical presentation but currently, we do not have early predictive fluid biomarkers available.

Although a series of studies have aimed at identification of specific biomarkers such as glial markers (calcium-binding astroglial protein, S100B) and axonal damage markers (phosphorylated neurofilament heavy subunit, tau protein) within the CSF for diagnostic as well as prognostic evaluations of inflammatory neuropathies such as GBS, the reliable markers are still lacking.[14]

Neurofilaments (Nfs) have aroused considerate attention in biomarker research in a variety of neurological disorders.

Nfs are the most abundant cytoskeletal component of mature neurons providing structural support, but they also control important cellular processes, such as axon conduction, distribution of organelles, and receptor recycling at the synapse.

Nfs are released in significant quantity following axonal damage or neuronal degeneration.[15] Disruption to the axonal membrane releases Nfs into the interstitial fluid and eventually into CSF and blood.

We can distinguish 4 subunits: Nf light (NfL), Nf medium (NfM), Nf heavy (NfH) chain, and alpha-internexin.

Neurofilament light chain (NfL) is of particular interest, and it is considered to be a marker of axonal damage in a variety of different neurological disorders, including traumatic, inflammatory, and neurodegenerative diseases.

Blood Nf levels could be useful for both predicting and monitoring disease progression and for assessing the efficacy and/or toxicity of future neuroprotective treatment strategies.[16]

In this regard, NfL was suggested in a recent study as a possible biomarker related to disability in these patients.[17] Another study[6] demonstrated that elevated CSF NfL concentrations at the onset of GBS may predict long-term disability. In addition, glial fibrillary acidic protein (GFAP) and S100B were investigated as possible prognostic biomarkers in the acute phase of GBS.[6]

In our present investigation of 19 patients, we investigated NfL, GFAP, and S100B in both CSF and plasma in patients with GBS. We have attempted to correlate these markers with the prognosis of GBS.

Methods

Study population

This is a retrospective study in which all patients with suspected diagnosis of GBS, including all its variants, from January 2009 to December 2019, were selected from our biobank.

All patients included met level 1 or 2 of the Brighton criteria.[18]

Extraction of clinical and paraclinical data

The following parameters were extracted from the electronic medical record: (i) sociodemographic variables such as age and gender; (ii) clinical variables such as evidence or not of previous infection and type of infection, clinical involvement at onset and symptoms at admission and at nadir, deep tendon reflexes at admission, respiratory function test results, modified Erasmus GBS outcome score (mEGOS) at admission, Hughes functional score (HFS) at admission, at nadir and at hospital discharge and Medical Research Council Sum Score (MRC-SS) at admission and at nadir; (iii) data on delay in admission from symptom onset, delay in performing lumbar puncture, and delay in performing electromyogram from symptom onset; (iv) results from the CSF analysis (cell count, total protein levels), presence of oligoclonal bands in CSF, and presence and type of antiganglioside antibodies in serum; (v) electrophysiological results according to the Hadden criteria; (vi) information on treatment strategies; (vii) total hospitalization time and ICU stay, and (viii) functional status 6 months after hospital discharge.

Analysis of neurofilament light chain, glial fibrillary acidic protein, and S100 protein concentrations in serum and cerebrospinal fluid

Subsequently, frozen CSF and serum samples were analyzed by an investigator blinded to clinical data using the Simoa 2-Plex B (NfL and GFAP) kit and the human S100B ELISA kit in the Simoa Quanterix SR-X Analyzer.

Statistical analyses

The descriptive statistical analysis includes the calculation of the mean and standard deviation or median in the case of continuous quantitative variables, and the calculation of frequencies and percentages in the case of qualitative variables.

To describe the association between the different biomarkers (NFLs in serum and CSF, GFAP in serum and CSF, S100B protein in serum and CSF) and the mEGOS score, the HFS score on admission, the MRC-SS score at nadir, and total hospitalization time and ICU time, the Pearson correlation coefficient was calculated.

Finally, analysis of variance (ANOVA) was used to determine the relationship between serum and CSF NfL levels and the different electrophysiological Hadden variants.

p Values $< .05$ were considered statistically significant.

The software used was SPSS version 29.

Ethical aspects

No personal data allowing patient identification were collected. All recorded data were previously anonymized.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Hospital General Universitario de Castellón (date of approval July 14, 2021).

Informed consent was requested from all patients included in the study.

This study is sponsored by the Asociación Neurológica de Castellón, which is responsible for its financing.

Results

Clinical and electrophysiological characteristics

A total of 19 cases have been included, 10 of which were male (52.6%). All patients fulfilled levels 1 or 2 of the Brighton diagnostic criteria regarding their clinical presentation: bilateral and flaccid weakness of the limbs, decreased or absent deep tendon reflexes, monophasic course, and no alternative explanation for their symptoms.

Out of these GBS patients, preceding infection was reported in 11 (58%), digestive infection in 7 cases and respiratory infection in 4.

With regard to the clinical involvement at baseline, 10 cases had motor symptoms (52.63%), 8 cases had both motor and sensitive symptoms (42.11%), and 1 case had weakness limited to cranial nerves (5.26%) (appendix Table 1).

The delay from symptom onset to hospital admission was 6.16 days (1–20).

Of the total number of patients, 6 had decreased deep tendon reflexes, 10 had absent, normal in 2 cases, and exalted in 1 case.

As for the electrophysiological GBS classification, 9 patients showed a primary demyelinating pattern (47.37%), 6 patients exhibited primary axonal changes (31.58%), 3 patients had equivocal abnormalities (15.79%), and was normal in only 1 case (5.26%).

Eleven (11) of 19 GBS patients showed albumin–cytological dissociation in the CSF (57.9%). The delay in performing lumbar puncture was 4.37 days (1–15), the same as for the collection of serum samples.

We found positive test results for anti-ganglioside antibodies in 4 patients only (21.05%) and negative test results for oligoclonal IgG bands in CSF in all cases in which they were tested.

Based on their clinical presentation, results from NCS and anti-ganglioside antibodies, we classified all 15 patients with primary demyelinating features as AIDP, 2 patients with primary axonal abnormalities on NCS as AMAN, 1 as AMSAN, and 2 cases as Miller–Fisher syndrome.

Clinical scores

The functional score on the HFS scale at admission was equal to 1 in 4 cases and ≥ 2 in the remaining patients.

The mean score on the MRC-SS at nadir was 48.83 (28–60).

As for the mEGOS, the mean score was 2.63 (0–8), being ≥ 5 in 3 cases only.

Treatment strategies

Of all patients, 17 were treated with IVIg (89.5%), without undergoing additional PE.

Functional outcome

Five patients were transferred to an ICU, with a mean stay of 13 days.

As for the mean number of total days of hospitalization, it was 67 days.

Functional outcome at 6 months after discharge was good in 12 patients (70.6%), while 5 of them (29.4%) required walking assistance. Two patients were lost to follow-up.

Of the total number of patients, none of them died of GBS.

NfL levels

The median NfL concentration was 512.2 pg/ml (4.47–2553.03) in serum (sNfL) and 11 161.6 pg/ml (162.83–88 998.14) in CSF.

GFAP levels

The median GFAP concentration was 258.8 pg/ml (43.92–791.98) in serum and 16 149.1 pg/ml (4461.78–44 493.59) in CSF.

S100B levels

The median S100B concentration was 168.1 pg/ml (27.24–1018.00) in serum and 452.8 pg/ml (138.20-1136.00) in CSF.

Correlation between NfL, GFAP, and S100B levels and disease severity

Disease severity was assessed with the HFS score at admission and MRC-SS score at nadir.

In relation to the HFS scale at admission, the results were not significant in all cases, thus not detecting relationships between the variables. Thus, higher biomarker levels were not related to higher values on the functional scale at admission.

Regarding the MRC-SS score at nadir, the correlation was negative, so that higher levels of biomarkers are related to lower scores on the score and greater clinical involvement. It was significant ($p < .05$) for serum NfL (Supplementary Fig. 1) and serum GFAP. The value of the Pearson correlation coefficient was −0.531 y–0.497, respectively.

Correlation between NfL, GFAP, and S100B levels and disease prognosis

We evaluated disease prognosis using the mEGOS score.

The correlation was significant ($p < .05$) in the case of NfL in serum and CSF (Supplementary Fig. 2) and GFAP in CSF, so that higher levels of the biomarkers are related to higher scores and worse prognosis. The value of the Pearson correlation coefficient between the variables was 0.472 for serum NfL, 0.576 for CSF NfL, and 0.544 for CSF GFAP.

Correlation between NfL, GFAP, and S100B levels and length of hospital and ICU stay

The results were not significant, and it could not be affirmed that higher levels of the biomarkers were related to a greater number of days of hospital stay or in the ICU.

Relationship between NfL levels and Hadden's electrophysiological variants

The mean serum NfL value was 204.16 pg/ml in the case of the demyelinating variant and 1145.74 pg/ml in the axonal variant, while it was 338.07 pg/ml in those cases that showed equivocal abnormalities and 5.44 pg/ml in the only case in which the electrophysiological study was normal. No significant differences were detected between groups ($p = .139$) using ANOVA.

In the case of NfL in CSF, the mean value was 2021.50 pg/ml in those with demyelinating pattern (SD 1966.29), 23 529.84 pg/ml in the axonal variant (SD 36 829.86), while it was 17 361.25 pg/ml in those with equivocal abnormalities (SD 21 283.80) and 614.95 pg/ml in the case in which the study was normal. Again, in the ANOVA test, no significant differences were detected between the different Hadden electrophysiological variants ($p = .334$).

Discussion

GBS is a dynamic, acute polyneuropathy causing damage in PNS with intrathecal structures involved.

Early and accurate recognition of GBS may be challenging in such a clinically heterogeneous disorder, especially when there are also alternative diagnoses possible.

Although the diagnosis of GBS is well-established by using clinical criteria with supportive electrophysiology and CSF investigations, a convenient and reliable biomarker for the prediction of clinical outcome or prognosis is still needed.

Without accurate biomarkers, the clinical features will remain the hallmark for the diagnosis of GBS. It is very important to carefully collect all clinical features of suspected cases of GBS to physicians, to be able to have all necessary clinical data available for classification.[18]

AIDP is the prototype of GBS. Macrophages from the blood invade the PNS and target at antigens on Schwann cells or the myelin sheath with the help of cytokines released from activated macrophages and T lymphocytes. They strip off intact myelin sheaths leading to demyelination.[8,19]

Edema in the nerve root is probably causing the phenomena of cyto–albumin dissociation because proteins with at least the size of 70 kDa as albumin cannot dissociate toward the blood compartment.[20] Cyto–albuminologic dissociation in CSF, commonly regarded as one of the hallmarks of GBS, was found in less than half of the patients when tested within the first day after the onset of weakness in a previous study[18] and only after a week of weakness, this finding reaches a sensitivity of 80%.

NfL having a molecular weight of 68 kDa may also not dissociate from and in the blood compartment explaining the high NfL levels in the CSF and serum in follow-up examinations.[21]

The source of NfL released into the CSF in patients with GBS is likely damaged proximal nerve roots which are surrounded by CSF in the subarachnoid space of the spinal cord[15] and may be influenced by the disruption of the blood–nerve barrier (BNB) and the blood–CSF barrier (BCB). However, extensive deterioration of BNB/BCB may also allow NfL released to peripheral blood from damaged peripheral nerves, to enter the CSF.[6]

In current literature, the potential of NfL as a biomarker in a variety of neurological diseases including neuropathies is being discussed.[13] One of the most attractive features of the Nfs is the long half-life in CSF (2–3 months).[22]

A recent study based on a sample of 25 patients with acquired neuropathies, including 5 cases of GBS, suggested NfL as a potential biomarker in correlation with the patients' disability.[17] Another study[6] with 18 patients showed that high NfL concentrations in CSF at the onset of GBS may predict long-term disability, thus, reflecting affirmatively on the mechanisms of axonal damage in this disease.

GFAP and S100B has been investigated previously in the acute phase of GBS as a prognostic CSF biomarker.[6] A previous study observed an increased level of S100B in CSF of GBS patients and a significant positive correlation between CSF S100B levels and the recovery time of GBS patients, indicating that S100B may be a prognostic marker of GBS.[14,23]

In our present investigation of 19 patients, we investigated NfL, GFAP, and S100B in both CSF and plasma in patients with GBS. We have attempted to correlate these markers with the prognosis of GBS.

In comparison with other studies on both blood and CSF-derived Nfs in GBS (2 studies on NfH and 1 on NfL) with sample sizes ranging from 3 to 27, our number of enrolled patients suggests reasonable validity.[6,13,17,24]

In our environment, the overall incidence of GBS patients is approximately 0.85–1.56/100 000 inhabitants per year.[25] Our tertiary hospital serves a population of about 300 000 inhabitants. Therefore, 19 patients in a total of 11 years could be considered a representative GBS population.

In this study, data were extracted from medical records retrospectively.

Clinical evaluation was performed with the MRC-SS, HFS, and the mEGOS.

Although recovery in GBS occurs primarily during the first 6 months, it may continue even beyond 12 months[26] and significant improvement has been recorded between 6 months (57%) and 12 or 24 months of follow-up (70% and 82%, respectively). In our patients recovery is achieved in 70.6% of the cases.

The median sNfL concentration on admission was 512.2 pg/ml, a much higher value in relation to other studies that reported a median of 84.7 pg/ml in acute neuropathies including 5 cases of GBS.[13,17]

Other studies have shown that doubling the sNfL concentration upon admission makes it almost 3 times more likely to have a less-favorable outcome (HFS$\geq$2) and that in addition higher sNfL levels on admission correlated strongly with duration of hospitalization[13] but we cannot conclude the same with our results.

Therefore, we confirm the finding of elevated levels of NfL, GFAP, and S100B in CSF and plasma in the acute phase of GBS.

We can point out that their value has a certain relationship with the severity of the disease and prognosis, and that in some way, they have an influence, but we would lack more information to make good predictions.

However, serum S100B protein levels are the only case in which we have not been able to correlate them with greater clinical severity or worse prognosis in the short- and long-term.

We have also found no relationship between NfL values and the rest of the markers and the duration of hospital stay in total and in the ICU. One reason for this may be that admission to ICUs often depends not only on the clinical characteristics of the patient, but also on the availability of beds and the pressure of care.

We can also report that NfL concentrations in both serum and CSF were higher in the cases that presented an axonal pattern in the electrophysiological study. However, we found no statistically significant differences between the different subgroups, perhaps due to the small sample size.

In conclusion, our systematic retrospective study verifies an increase in NfL levels in not only CSF but also in plasma in the acute phase of GBS and, although we found some relationship between the different markers and severity and prognosis in these patients, unfortunately, our data do not allow us to state that NfL levels detected early in the serum of patients with GBS can allow individualized risk stratification and prognosis.

As a possible limitation of the study, we would point out the retrospective extraction of information from the patients' clinical histories, with the possible biases and lack of information in some cases that this entails.

Future prospective studies incorporating detailed longitudinal clinical and electrophysiological assessments, and sampling are clearly warranted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2024.100173.

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Patient consent

Informed consent was requested from all patients included in the study.

Ethical considerations

No personal data allowing patient identification were collected. All recorded data were previously anonymized.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Hospital General Universitario de Castellón (date of approval July 14, 2021).

Declaration of competing interest

The authors of the article entitled: "Early prognostic factors in Acute Inflammatory Demyelinating Polyneuropathy: role of neurofilaments" declare that neither the article nor any part of it has been duplicated or sent elsewhere. The manuscript is true and has been approved by all authors. Furthermore, each of the authors believes that the article represents honest work.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Hospital General Universitario de Castellón (date of approval July 14, 2021).

There is no conflict of interest in relation to the article.

Appendix Table

Table 1 Baseline clinical characteristics at admission.

Patient N°	Sex	Age	Previous infection	Clinical involvement	DTR
1	F	67	Respiratory	Sensitive + Weakness	Normal
2	M	66	None	Weakness	Absent
3	M	17	Digestive	Weakness	Decreased
4	M	25	Digestive	Weakness	Absent
5	M	54	Digestive	Sensitive + Weakness	Absent
6	F	50	Digestive	Sensitive + Weakness	Absent
7	M	77	None	Weakness	Absent
8	F	21	Respiratory	Weakness	Decreased
9	M	52	None	Sensitive + Weakness	Absent
10	F	72	Digestive	Weakness	Exalted
11	M	32	None	Weakness	Absent
12	M	59	Digestive	Sensitive + Weakness	Decreased
13	M	63	Respiratory	Cranial	Absent
14	F	48	None	Weakness	Decreased
15	F	74	Respiratory	Sensitive + Weakness	Absent
16	M	45	None	Sensitive + Weakness	Absent
17	F	65	None	Weakness	Normal
18	F	74	None	Sensitive + Weakness	Decreased
19	F	26	Digestive	Weakness	Decreased

DTR: deep tendon reflexes, M: male, F: female.

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