RESEARCH ARTICLE

CSF Findings in Relation to Clinical Characteristics, Subtype, and Disease Course in Patients With Guillain-Barré Syndrome

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Abstract

Background and Objectives

To investigate CSF findings in relation to clinical and electrodiagnostic subtypes, severity, and outcome of Guillain-Barré syndrome (GBS) based on 1,500 patients in the International GBS Outcome Study.

Methods

Albuminocytologic dissociation (ACD) was defined as an increased protein level (>0.45 g/L) in the absence of elevated white cell count (<50 cells/μL). We excluded 124 (8%) patients because of other diagnoses, protocol violation, or insufficient data. The CSF was examined in 1,231 patients (89%).

Results

In 846 (70%) patients, CSF examination showed ACD, which increased with time from weakness onset: ≤4 days 57%, >4 days 84%. High CSF protein levels were associated with a demyelinating subtype, proximal or global muscle weakness, and a reduced likelihood of being able to run at week 2 (odds ratio [OR] 0.42, 95% CI 0.25–0.70; $p = 0.001$) and week 4 (OR 0.44, 95% CI 0.27–0.72; $p = 0.001$). Patients with the Miller Fisher syndrome, distal predominant weakness, and normal or equivocal nerve conduction studies were more likely to have lower CSF protein levels. CSF cell count was <5 cells/μL in 1,005 patients (83%), 5–49 cells/μL in 200 patients (16%), and ≥50 cells/μL in 13 patients (1%).

Discussion

ACD is a common finding in GBS, but normal protein levels do not exclude this diagnosis. High CSF protein level is associated with an early severe disease course and a demyelinating subtype. Elevated CSF cell count, rarely ≥50 cells/μL, is compatible with GBS after a thorough exclusion of alternative diagnoses.

Classification of Evidence

This study provides Class IV evidence that CSF ACD (defined by the Brighton Collaboration) is common in patients with GBS.

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Glossary

ACD = albuminocytologic dissociation; **CSF-TP** = CSF total protein; **GBS** = Guillain-Barré syndrome; **GBS-DS** = GBS disability score; **Ig** = immunoglobulin; **IGOS** = International GBS Outcome Study; **IQR** = interquartile range; **LP** = lumbar puncture; **MFS** = Miller Fisher syndrome; **MRC** = Medical Research Council; **NCS** = nerve conduction study; **OR** = odds ratio; **PE** = plasma exchange.

In 1916, Guillain et al.[1] reported 2 patients with acute flaccid paralysis with a normal CSF cell count and an elevated protein level—also referred to as albuminocytologic dissociation (ACD)—identifying what has come to be known as the Guillain-Barré syndrome (GBS). The diagnosis of GBS relies on the clinical examination and is supported by both neurophysiologic and CSF findings. The classic ACD is also used in the current diagnostic criteria for GBS.[2-4] However, the diagnostic value of ACD has been previously debated, and a strict definition of ACD is lacking.[5,6] The CSF total protein (CSF-TP) level is known to be normal in some patients, especially when the lumbar puncture (LP) is performed early in the disease course.[5,7,8] Moreover, previous studies have suggested that some patients with GBS may have an increased cell count.[5,8]

The proximity of the nerve roots to the CSF makes the latter a potential source of disease-related biomarker for GBS. In fact, in routine practice, CSF-TP and cell count remain the only laboratory examinations widely available. Increased CSF-TP levels have been validated as a diagnostic criterion for GBS and may represent blood-nerve barrier disruption, an increased intrathecal antibody synthesis, or both.[8,9] Several studies have suggested that CSF-TP is related to disease severity and prognosis.[10-12] Furthermore, studies have shown a possible relation between CSF-TP, clinical variants, and electrophysiologic subtypes of GBS.[6,12]

Although ACD has played an important historical role in the diagnosis of GBS, the value of ACD in the 21st century is less certain because it is increasingly appreciated that some patients with GBS may have a normal CSF-TP level and/or elevated cell counts. The primary research questions addressed in this study encompass the variation of CSF-TP level and CSF cell count in GBS and how these are related to the clinical characteristics and variants, electrophysiologic subtypes, disease severity, and outcome.

Methods

Study Design

The study was conducted using data from the International GBS Outcome Study (IGOS), a prospective observational cohort study, where clinical data are collected on newly diagnosed patients with GBS from disease onset throughout at least 1 year, with the goal of identifying determinants of disease progression and recovery.[13,14] This study was based on the first 1,500 IGOS patients (IGOS-1500 cohort) who had confirmed GBS according to the National Institute of Neurological Disorders and Stroke diagnostic criteria and for whom CSF data were available.[2,3,15]

Standard Protocol Approvals, Registrations, and Patient Consents

IGOS was approved by the review board of Erasmus University Medical Center, Rotterdam, The Netherlands (MEC-2011-477) and the local institutional review boards of participating hospitals or universities. Written informed consent was obtained from all patients or their legal representatives.

Data Collection

Data regarding demographics and neurologic symptoms and signs were collected at study entry and at weeks 1, 2, 4, 8, 13, 26, and 52, in conformity with the IGOS study protocol.[14] The results of CSF examination, including CSF-TP levels, cell count, and erythrocytes, were collected at study entry. All CSF analyses were conducted in the local centers as part of routine clinical care. We defined ACD as an elevated CSF-TP value >0.45 g/L in combination with a CSF cell count <50 cells/μL, per the criteria developed by the Brighton Collaboration,[3] and categorized CSF cell count into 4 distinct groups: <5 (normal), 5–10, 11–49, and ≥50 cells/μL.[8,16] To assess whether patients with a CSF cell count ≥50 cells/μL had an otherwise typical GBS phenotype or comprised a distinct subgroup, we compared their clinical and electrophysiologic characteristics with the characteristics of patients with GBS with a normal cell count and patients with a mild pleocytosis (5–49 cells/μL). CSF cell count was corrected for the number of erythrocytes in the CSF in the ratio 1:700, according to reference values for peripheral blood leukocytes and erythrocytes.[17,18] In patients with ≥50 cells/μL in the CSF, the local investigator was contacted to confirm this finding and give details on additional diagnostics that were performed and the clinical course. The time to LP was defined as the number of days from onset of weakness to LP and was defined as early when performed within 4 days from onset and late when performed after 4 days from onset. We defined disability using the GBS disability score (GBS-DS) and muscle strength using the MRC sum score.[19,20] If data on the GBS-DS was missing at week 26 or 52, the GBS-DS from the previous visit was used for patients with a GBS-DS ≤2. We used data from the first nerve conduction study (NCS), local reference values, and a computer algorithm to classify patients as demyelinating, axonal, inexcitable, equivocal, or normal per the Hadden criteria.[21] We defined the GBS clinical variant as per the clinical evaluation of the local site investigator at the week 2 visit or (if unavailable) per week 1 or entry visit data. The presence of

autonomic dysfunction was defined as cardiac, blood pressure, gastroenteric, bladder, pupil, or other autonomic abnormality, as assessed by the evaluating local site investigator. Treatment was defined based on the first treatment episode reported in the IGOS dataset.

Data Analyses

We investigated the relationship between CSF-TP level and CSF cell count and demographics, timing of LP, antecedent events, clinical phenotype, and electrophysiologic subtype. In addition, we investigated the relation between CSF-TP levels and the distribution of muscle weakness. We used the bilateral MRC scores for the shoulder abductors and wrist extensors to classify weakness in the arms and likewise for the hip flexors and ankle dorsiflexors to classify weakness in the legs.[22] We classified "distribution of muscle weakness" into 5 distinct categories: (1) proximal weakness (i.e., proximal-predominant weakness in both arms and legs, defined as a difference of ≥2 points in the MRC sum score of proximal vs distal muscles), (2) distal weakness (i.e., distal-predominant weakness in both arms and legs, defined as a difference of ≥2 points in the MRC sum score of proximal vs distal muscles), (3) mixed weakness (i.e., proximal weakness in the arms and distal weakness in the legs or vice versa), (4) global weakness (i.e., a difference of <2 points in the MRC sum score of proximal vs distal muscles), and (5) no weakness (i.e., no weakness of the investigated muscles). Furthermore, we examined the relation between CSF-TP levels and disease outcome, as indicated by the need for mechanical ventilation, reaching GBS-DS ≤2 or GBS-DS ≤1 at weeks 2, 4, and 26.[19] All analyses of CSF-TP were corrected for the time to LP and treatment before or after LP, as previous studies reported that CSF-TP level increases with increasing time to LP and may also increase after treatment with IV immunoglobulin (Ig).[8,23]

Previous studies showed that patients with GBS from Bangladesh have distinctive clinical characteristics and outcome and limited treatment compared with those from other geographic regions. Therefore, the 164 patients from Bangladesh were also analyzed separately with data provided in eTables 1 and 2 (links.lww.com/WNL/C766).

Data were analyzed using IBM SPSS Statistics for Windows, version 25, and graphs were generated in GraphPad Prism for Windows, version 8. Continuous data were presented as median (interquartile range [IQR]) or (95% CI) and were compared using the Mann-Whitney *U* test or Kruskal-Wallis test. Categorical data were presented as numbers (%) and compared using the χ^2 test or Fisher exact test. Logistic regression analyses were used to describe the association between CSF-TP levels and outcome, thereby correcting for a predefined number of potential confounding factors. To improve the readability of some of the graphs, we applied the Tukey test to remove outliers. The Spearman rank correlation (r_s) was used to evaluate correlations. A 2-sided p value <0.05 was considered significant; the value of a significant findings was based on 95% CIs.

Data Availability

Data collected in IGOS will be used initially for planned research projects conducted by the IGOS Consortium. Data can be made available by the IGOS Steering Committee on reasonable request for specific research projects. Data are not publicly available because they contain information that could compromise the privacy of patients.

Results

Characteristics of the Cohort

From the IGOS-1500 cohort, we excluded 85 patients (6%) because an alternative diagnosis was established during follow up, 32 (2%) because of a protocol violation, and 7 (0.5%) because no data were entered, similar to earlier published IGOS data reports.[13] In the remaining 1,376 patients, LP was performed, and the CSF was examined in 1,231 patients (89%). As per protocol, data on multiple LPs were not available. Patients were enrolled between April 2012 and May 2017 from 155 centers across 19 countries on 6 continents.

Table 1 summarizes the baseline characteristics of the study cohort (n = 1,231). The median age was 50 years (IQR 33–64), and 60% were male patients. The median CSF-TP was 0.67 g/L (IQR 0.41–1.21), and the median time from onset of weakness to LP was 4 days (IQR 2–7).

The proportion of patients with an elevated CSF-TP level (>0.45 g/L) was 70%, and this was dependent on the timing of LP. Only 52% of patients had an elevated CSF-TP level by day 3 and 86% of patients at day 7 (Figure 1). The CSF cell count was <5 cells/μL in 1,005 patients (83%) and 5–49 cells/μL in 200 patients (16%). In 13 patients (1%), ≥50 cells/μL, ranging from 53 to 231 cells, were reported (Table 2). Elevated CSF-TP was more frequently found in male (73%) than in female (66%) patients (Table 1).

As per the Brighton criteria, ACD was present in 70% of patients.[3] Based on the Asbury and Cornblath criteria, where cell counts ≤10 cells/μL are considered compatible with typical GBS, 785 patients (64%) within the IGOS cohort fulfilled the definition of ACD (with CSF-TP >0.45 g/L).[2] In addition, when we used a cutoff of <5 cells/μL, which is commonly used in clinical practice to define a normal CSF cell count, 56% (n = 683) fulfilled the definition of ACD.[8,16] Finally, 50% of patients had elevated CSF-TP levels when applying the age-specific reference values (Table 2).[24]

Clinical and Neurophysiologic Characteristics in Relation to CSF-TP Levels

Initial analysis of the relation between CSF-TP levels and clinical severity showed an association between higher CSF-TP levels and the presence of facial weakness, which persisted after correcting for time to LP (Table 1). Oculomotor weakness at entry was associated with lower CSF-TP level (0.49 g/L (95% CI 0.44–0.57)). Of patients with oculomotor

Table 1 Baseline Clinical and Neurophysiologic Characteristics in the IGOS-1500 Cohort and in Relation to CSF-TP

	IGOS-1500 cohort	CSF-TP ≤0.45 g/L	CSF-TP >0.45 g/L	*p* Value
N	1,231	367 (30)	862 (70)	
Age, y	50 (33–61)	51 (48–54)	50 (49–52)	0.413
Sex				0.004[a]
Male	737 (60)	197 (53)	539 (63)	
Female	494 (40)	170 (46)	323 (38)	
Continent of inclusion				0.015[a]
Africa	29 (2)	8 (2)	21 (2)	
Asia	263 (21)	56 (15)	207 (24)	
Europe	693 (56)	228 (62)	465 (54)	
North America	182 (15)	59 (16)	122 (14)	
Oceania	7 (1)	3 (1)	4 (1)	
South America	57 (5)	14 (4)	43 (5)	
Antecedent events (all)	967 (79)	304 (83)	661 (77)	0.013[a]
Gastroenteritis	341 (28)	105 (29)	236 (27)	
Upper respiratory tract infection	480 (39)	169 (46)	310 (36)	
Time to LP, d		3 (3–4)	5 (5–6)	<0.001[a]
MRC sum score	47 (34–54)	48 (47–50)	47 (46–48)	0.015[a]
Cranial nerve involvement	592 (48)	171 (47)	421 (49)	0.310
Oculomotor		83 (23)	100 (12)	
Facial weakness		98 (27)	269 (31)	
Bulbar weakness		93 (25)	217 (25)	
Mechanical ventilation	213 (17)	72 (20)	140 (16)	0.152
ICU admission	324 (26)	108 (30)	215 (25)	0.102
Autonomic dysfunction	290 (24)	91 (25)	198 (23)	0.523
Sensory deficits	700 (57)	167 (54)	501 (59)	0.246
Pain	651 (53)	165 (45)	485 (57)	<0.001[a]
Clinical variant				
Sensorimotor	713 (61)	192 (55)	519 (63)	<0.001[a]
Pure motor	271 (23)	69 (20)	202 (24)	
MFS	77 (7)	36 (11)	38 (5)	
MFS-GBS overlap	63 (5)	30 (9)	33 (4)	
Other	56 (5)	20 (6)	36 (4)	
Hadden electrophysiology classification				
Demyelinating	480 (55)	114 (44)	365 (60)	<0.001[a]
Axonal	78 (9)	24 (9)	54 (9)	
Inexcitable	26 (3)	10 (4)	16 (3)	
Equivocal	238 (27)	90 (35)	148 (24)	
Normal	46 (5)	23 (9)	23 (4)	

Continued

Table 1 Baseline Clinical and Neurophysiologic Characteristics in the IGOS-1500 Cohort and in Relation to CSF-TP *(continued)*

	IGOS-1500 cohort	CSF-TP ≤0.45 g/L	CSF-TP >0.45 g/L	*p* Value
Distribution of weakness				
Global weakness	797 (65)	214 (59)	582 (68)	<0.001[a]
Proximal weakness	172 (14)	46 (13)	125 (15)	
Distal weakness	110 (9)	36 (10)	74 (9)	
No weakness	134 (11)	63 (17)	71 (8)	
Treatment				
IVIg	903 (73)	291 (79)	610 (70)	0.101
Plasma exchange	94 (8)	23 (6)	71 (8)	
Treatment initiated before LP	116 (12)	25 (7)	89 (10)	0.024[a]

Abbreviations: CSF-TP = CSF total protein; GBS = Guillain-Barré syndrome; ICU = intensive care unit; Ig = immunoglobulin; IGOS = International GBS Outcome Study; LP = lumbar puncture; MFS = Miller Fisher syndrome; MRC = Medical Research Council.
Data are median (95% CI) and n (%).
For continuous variables, the Mann-Whitney *U* test was applied to test the association between clinical characteristics and CSF-TP. For categorical variables, the χ^2 test was applied.
[a] $p < 0.05$.

involvement at study entry, 70% had either the Miller Fisher syndrome (MFS) or MFS-GBS overlap variant. Patients with MFS had the lowest levels of CSF-TP (median 0.45 g/L, 95% CI 0.40–0.52), whereas the highest levels were found in patients with sensorimotor GBS (median 0.71 g/L, 95% CI 0.68–0.78) and the pure motor variant (median 0.70 g/L, 95% CI 0.64–0.83), which persisted after correcting for timing of LP ($p < 0.001$). The proportion of patients with elevated CSF-TP (>0.45 g/L) was 73% in sensorimotor GBS, 75% in pure motor GBS, 50% in MFS, and 52% in MFS-GBS overlap variant.

The CSF-TP varied according to the distribution of muscle weakness (Figure 2). Patients with global weakness or proximal-predominant weakness more often had elevated CSF-TP levels (73%) than patients with distal predominant weakness (67%). Three-quarters of patients who reported pain at study entry had elevated CSF-TP levels compared with 65% of the other patients ($p < 0.001$).

The demyelinating subtype was associated with higher CSF-TP levels (median 0.80 g/L, 95% CI 0.72–0.88). Lower CSF-TP levels were found in patients with the equivocal subtype (median 0.53 g/L, 95% CI 0.48–0.58) or normal NCS (median 0.45 g/L, 95% CI 0.38–0.52), also after correcting for time to LP and treatment before LP (Table 1). Elevated CSF-TP levels were found in 76% of patients with demyelinating subtype vs 69% of patients with axonal subtype of GBS.

Treatment with either IVIg or plasma exchange (PE) did not differ between patients with or without elevated CSF-TP levels, but more patients with elevated CSF-TP levels received treatment before the LP was performed (Table 1). Median CSF-TP levels were significantly higher when treatment was initiated before the LP (1.01 g/L [95% CI 0.69–1.15]) vs after (0.62 g/L [95% CI 0.59–0.68]; $p < 0.001$). However, time to LP was also longer in patients who received treatment before LP, and these patients were more severely affected, as reflected by lower MRC sum scores at entry. After correcting for time to LP, there was no significant difference in the median CSF-TP between patients who received treatment before or after LP (Table 3).

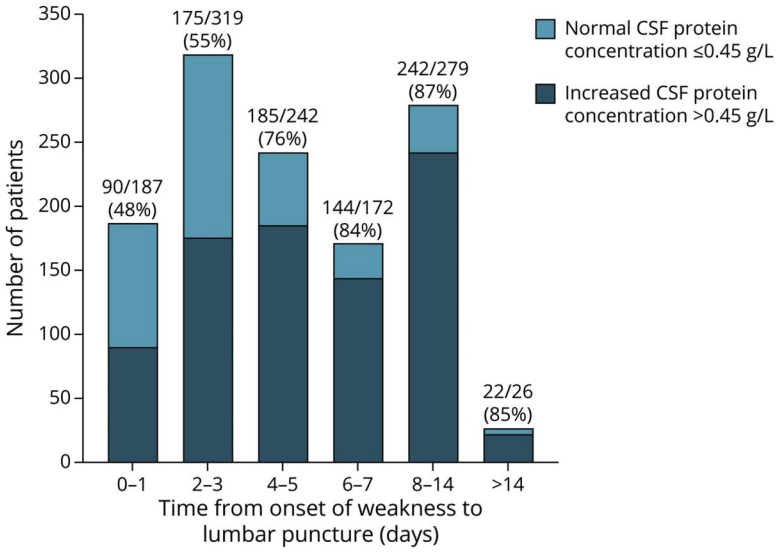
CSF Cell Count and Relation to Clinical and NCS Characteristics

Higher CSF-TP levels correlated with an increased CSF cell count ($r_s = 0.133$, $p < 0.001$; Figure 3). The CSF cell count was not associated with time to LP, geographical area, antecedent events, sensory deficits, distribution of weakness, or cranial nerve involvement.

When comparing patients with <5 cells/μL with those with 5–49 and ≥50 cells/μL, no statistically significant differences in sex, age, or clinical characteristics were found. Although not significant, patients with ≥50 cells/μL seemed slightly younger, reported fewer antecedent events, had more severe disease, and a worse outcome as defined by the MRC sum score at entry, proportion requiring mechanical ventilation, and GBS-DS at 6 months and 1 year (eTable 3, links.lww.com/WNL/C766).

Thirty-one percent of patients who received IVIg before LP had a CSF cell count of 5–49 cells/μL vs 17% of patients who did not receive IVIg or received IVIg after the LP. The proportion of patients with ≥50 cells/μL was comparable in both groups, that is, 3% of patients who received IVIg before LP and 1% of patients who did not receive IVIg or received IVIg after the LP.

Figure 1 Time to LP and CSF-TP



Number/total (%) of patients (y-axis) with increased CSF protein concentration (>0.45 g/L) in relation to timing of lumbar puncture after onset of weakness (x-axis). CSF-TP = CSF total protein; LP = lumbar puncture.

Clinical characteristics of the 13 patients with a CSF cell count ≥50 cells/μL are summarized in eTable 3 (links.lww.com/WNL/C766). Ten of the 13 patients were followed up for at least 1 year (range 1–3 years) with no evidence of other diagnosis, whereas 3 patients were lost to follow-up early (between entry and week 2). Sensorimotor GBS was the predominant clinical variant (n = 8). NCS was performed in 8, of whom 5 had a demyelinating subtype. All were treated with IVIg, and 3 of the LPs were conducted after the treatment was initiated. For 1 of these 3 patients, the treating neurologist considered the elevated cell count to be related to the IVIg treatment. Data for this patient reported the presence of muscle pain and radicular pain in the lower legs from entry to week 2, but no signs of aseptic meningitis.[25] For 1 other patient, the entry assessment, which was performed 2 days after the start of IVIg, reported severe meningism. In the last patient, it was unknown whether the elevated CSF cell count was related to the IVIg treatment, and no pain was reported. In 10 of these 13 patients, the CSF was tested for infections (with various tests as decided by the local physician). In 8 of these 10 patients, no infectious etiology was found in the CSF. One patient (#12), with a CSF cell count of 63 cells/μL, was HIV infected with poor virologic control and ongoing immunosuppression despite combined antiretroviral therapy. The CSF of this patient was not tested for HIV. Because this patient presented with a demyelinating pattern on NCS, had no sicca symptoms or systemic lymphadenopathy, had a normal chest X-ray, and showed substantial recovery after 1 year, GBS was considered the most likely diagnosis. In the second patient (#4), with a CSF cell count of 99 cells/μL, initial analysis of the CSF showed abnormal titers for different serotypes of Coxsackie virus and Echovirus. On repeat analysis of the CSF 9 days later, titers for only one of the Coxsackie virus serotypes were still abnormal, and the CSF cell count had decreased to 73 cells/μL. The NCS was classified as acute motor sensory axonal neuropathy.

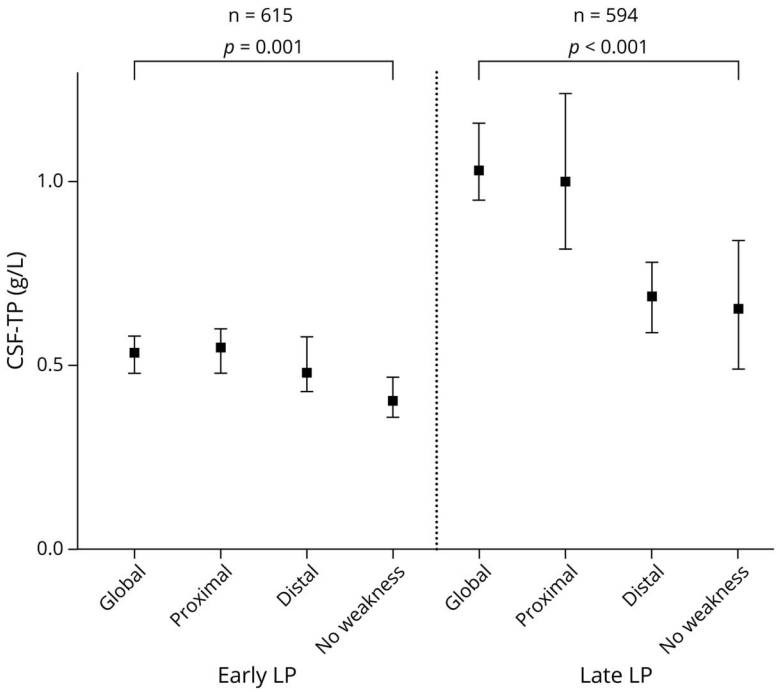
According to the Brighton criteria, which ranges from a high (level 1) to a low level (level 4) of diagnostic certainty of GBS, patients with a CSF cell count ≥50 cells/μL were all classified as level 3 because of the high cell count.[3]

Table 2 Proportion Fulfilling the Definition of Albuminocytologic Dissociation Based on Different Criteria Sets (N = 1,218)

		CSF leukocytes		
CSF-TP	**All**	**<50 (Brighton criteria)**	**≤10 (Asbury and Cornblath)**	**<5[a]**
>0.45 g/L	862 (70)	846 (70)	785 (64)	683 (56)
Elevated above age-related reference value[b]	616 (50)	606 (49)	557 (45)	480 (39)

Abbreviation: CSF-TP = CSF total protein.
Data are n (%).
[a] Commonly used in clinical practice.
[b] Age-related reference values: 30 days–14 years: 0.15–0.45 g/L, 14–30 years: 0.15–0.50 g/L, 30–50 years: 0.15–0.60 g/L, 50–80 years: 0.20–0.70 g/L, 80–200 years: 0.20–0.75 g/L.[24]

Figure 2 Distribution of Weakness and CSF-TP



Median (box) with 95% CIs (whiskers) CSF-TP in the distribution of muscle weakness in 1,226 patients with Guillain-Barré syndrome stratified for the timing of LP as defined by the median time to LP in the cohort (early ≤4 days, late >4 days). Distribution was defined by bilateral MRC sum scores in shoulder abductors, wrist extensors, hip flexors, and ankle dorsiflexors. Comparison of CSF-TP across the groups with a different distribution of muscle weakness with the Kruskal-Wallis test yields the *p* value <0.01. Early LP global, n = 382; proximal, n = 98; distal, n = 59; no weakness, n = 76. Late LP global, n = 412; proximal, n = 73; distal, n = 51; no weakness, n = 58. CSF-TP = CSF total protein; LP = lumbar puncture; MRC = Medical Research Council.

However, all these patients had bilateral and flaccid weakness of the limbs with a monophasic disease course, had areflexia, and progressed to a clinical nadir in less than 28 days. The CSF-TP levels were elevated in 9 patients, and NCS findings were consistent with one of the subtypes of GBS in 7 patients (88%).

Prognostic Value of CSF-TP Levels

Patients who were unable to walk independently (GBS-DS >2) after 2 and 4 weeks of study entry had higher CSF-TP levels compared with those who were able to walk independently (GBS-DS ≤2). In addition, patients unable to run (GBS-DS >1) had higher CSF-TP levels compared with patients able to run at weeks 2, 4, and 26. Logistic regression analyses were conducted to evaluate the effect of CSF-TP level on outcome when correcting for potential confounding factors (age, time to LP, MRC sum score at entry, preceding gastroenteritis, CSF cell count, GBS clinical variant, and treatment initiated before LP). Higher CSF-TP level was associated with lower odds of being able to run at week 2 (odds ratio [OR] 0.44, 95% CI 0.27–0.72; p = 0.001) and week 4 (OR 0.51, 95% CI 0.37–0.71; $p < 0.001$), also after correcting for potential confounders. In addition, this held true for the ability to walk independently at week 2 (OR 0.78, 95% CI 0.62–0.98; Table 4). CSF-TP level was neither an independent predictor for the ability to walk or run beyond week 4 nor for the risk of needing mechanical ventilation.

Classification of Evidence

This study provides Class IV evidence that CSF ACD (defined by the Brighton Collaboration) is common in patients with GBS.

Discussion

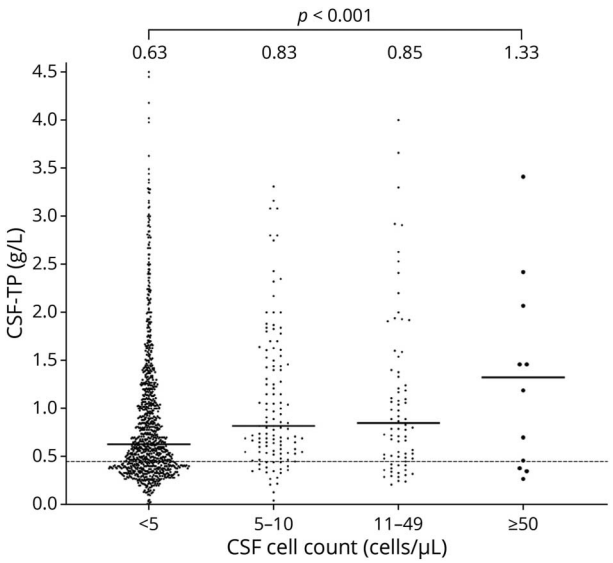
This study described the CSF properties in 1,231 patients with GBS in relation with clinical characteristics, severity,

Table 3 Treatment and CSF Properties

	Treatment before LP (n = 116)	Treatment after LP (n = 897)	*p* Value
Time to LP	8 (8–10)	3 (3–4)	<0.001
MRC sum score at entry	39 (34–44)	48 (48–50)	<0.001
CSF-TP			
All	n = 116 1.01 (0.69–1.15)	n = 897 0.62 (0.59–0.68)	<0.001
Early LP	n = 22 0.60 (0.48–1.07)	n = 552 0.50 (0.48–0.54)	NS
Late LP	n = 93 1.04 (0.72–1.25)	n = 342 0.90 (0.82–1.00)	NS
CSF cell count			
<5	81 (71)	720 (81)	0.058
5–10	20 (18)	96 (11)	
11–50	10 (9)	61 (9)	
≥50	3 (3)	10 (1)	

Abbreviations: CSF-TP = CSF total protein; LP = lumbar puncture; MRC = Medical Research Council.
Data are median (95% CI) or n (%).
Early LP ≤4 days, late LP >4 days.

Figure 3 CSF-TP and Cell Count



Grouped scatterplot of CSF-TP (y-axis) in relation to categories of CSF cell count (x-axis) in 1,194 patients with Guillain-Barré syndrome. Line and number indicate the median CSF-TP. Grid line at y = 0.45 g/L. Tukey methods have been applied to remove outliers. Comparison of distribution of CSF-TP across the groups with the Kruskal-Wallis test yields the *p* value <0.001. CSF-TP = CSF total protein.

NCS subtypes, and outcome. Depending on the definition, ACD was present in 50%–70% of IGOS patients. High CSF-TP levels were related to male sex, later performance of LP, sensorimotor variant, and demyelinating NCS subtype and predicted a poorer short-term outcome. In most patients, the CSF cell count was <5 cells/μL, but 16% had 5–49 cells/μL and 1% had ≥50 cells/μL with an otherwise typical GBS phenotype.

In line with previous reports, this study found an association between CSF-TP levels and time between onset of symptoms and LP.[6,8,26] Male patients had higher CSF-TP levels than female patients, possibly due to a difference in baseline CSF-TP levels between male and female individuals in general, but it may also represent a higher level of serum albumin in male patients.[24,27] Some hospitals use age-adjusted CSF-TP cutoff values but because of the variation in definitions and usage in current clinical practice, we have largely focused in our analysis on CSF-TP as a continuous variable.

Patients with the sensorimotor clinical variant of GBS showed the highest CSF-TP levels, while the lowest levels were found in patients with MFS, consistent with previous studies that have described CSF features in patients with MFS. In a retrospective study of 507 patients with GBS and 164 patients with MFS from 4 countries in Asia, patients with GBS were more likely to have elevated CSF-TP levels compared with those with MFS.[28,29]

Patients who received treatment with IVIg or PE before LP had higher CSF-TP levels. In a review of the mechanisms of action of IVIg in acute and chronic demyelinating neuropathies, a 2-fold increase in CSF-TP levels was observed after IVIg treatment as IgG enters the CSF.[23] In our study, patients who received treatment before the LP also had longer time to LP, complicating the interpretation of these results. When correcting for time to LP, no significant difference in the median CSF-TP was found between patients who received treatment before vs after LP, but this could be explained by the limited sample size of this subgroup. Higher CSF-TP levels in these patients may reflect a combination of increased IgG levels in the CSF caused by IVIg and a delay to LP. More patients who received treatment before LP had a CSF cell count ≥5 cells/μL compared with those who received treatment after LP, possibly reflecting an inflammatory response, as described in patients of IVIg-induced aseptic meningitis, an identified adverse event in 0.6%–1% of patients treated with IVIg.[25] Of the patients with ≥50 cells/μL within the IGOS cohort, 3 (23%) received treatment before LP, and in 2 of these patients, a relation with IVIg was suspected.

Lower CSF-TP level was an independent predictor of better short-term outcome at weeks 2 and 4. A recent study on 94 patients with GBS found that CSF-TP levels did not vary between ventilated and nonventilated patients.[30] By contrast, in a previous retrospective study that described CSF-TP levels in 36 patients with GBS, ventilated patients had 2-fold higher protein levels than nonventilated patients, although this difference was not statistically significant, probably because of limited sample size.[11] A study of 23 children with GBS found that CSF-TP could be used as a prognostic factor, with a protein level >1.00 g/L being predictive of a more rapid

Table 4 Association Between Higher CSF-TP and Outcome at Weeks 2, 4, and 26

	Week 2 (N = 959) OR[a] (95% CI)	Week 4 (N = 954) OR[a] (95% CI)	Week 26 (N = 851) OR[a] (95% CI)
Ability to walk	0.78[b] (0.62–0.98)	0.89 (0.77–1.05)	0.90 (0.76–1.06)
Ability to run	0.44[c] (0.27–0.72)	0.51[c] (0.37–0.71)	0.92 (0.80–1.06)

Abbreviations: CSF-TP = CSF total protein (continuous); MRC = Medical Research Council; OR = odds ratio.
[a] Logistic regression model adjusted for variables: MRC sum score at entry, age, preceding diarrhea, time to lumbar puncture, CSF cell count, treatment before lumbar puncture, and clinical variant.
[b] $p = 0.034$.
[c] $p \leq 0.001$.

disease evolution, more complications, and the need for mechanical ventilation, which could not be replicated in our study, neither in the entire cohort nor in the pediatric subgroup (younger than 18 years, n = 102, data not shown).[12] Another study on 24 patients with GBS showed a better outcome, as assessed by a higher MRC sum score in patients with lower CSF-TP levels in the acute phase of the disease and, unlike our study, after 6 months of follow-up.[31]

While our data show that CSF-TP level may provide some prognostic information in the early phases of the disease, it does not seem to be a sensitive biomarker of GBS because (1) its value is dependent on multiple factors, including the timing of LP and the GBS clinical variant and NCS subtype, and (2) one-third (or more, depending on the cutoff value) of the patients with GBS were shown to have normal CSF-TP levels. The CSF-TP level may represent an abnormal blood-nerve barrier permeability or an increased intrathecal antibody production. In addition, elevated CSF-TP levels also have been found in other demyelinating and inflammatory polyradiculoneuropathies, such as chronic inflammatory demyelinating polyneuropathy, sarcoidosis, HIV, and myelitis and may not be specific for GBS. Future IGOS studies will assess the diagnostic and prognostic values of more specific disease biomarkers, such as the CSF/serum albumin ratio, serum, or CSF neurofilament light chain or CSF sphingomyelin levels.[32-34] No data were available on the result of repeated LP in IGOS. In our view, normal CSF-TP should not be regarded as an argument to repeat LP in a patient suspected of GBS because of the limited diagnostic value of CSF-TP level and the possibility that this level may be influenced by the first LP.

The CSF cell count is mainly used to exclude other diagnoses in the context of GBS. This study confirmed that a CSF cell count ≥50 cells/μL is rare but can occur in up to 1% of patients with GBS. Pleocytosis in GBS has also been described in previous reports.[28,35-37] Based on results from additional investigations and the disease course, GBS was considered the most likely diagnosis in these patients, and most would have fulfilled the highest level of diagnostic certainty of the Brighton criteria, if not for the high cell count.

Our data suggest that, although an elevated CSF cell count is a rare finding in GBS and should be regarded a red flag, it may be compatible with the GBS diagnosis after a thorough exclusion of alternative diagnoses and careful follow-up. The term "ACD" has played a central role in GBS from the early days. Even then, the definition and presence of ACD was widely discussed in relation to GBS.[5] We still wonder—is it relevant to use the term ACD? In the literature, several definitions of elevated cell count in relation to ACD have been reported.[2,8,16] Likewise, there is little consensus on the definition of elevated protein levels. In validation studies of the current diagnostic criteria from the Brighton collaboration, level 1 criteria of diagnostic certainty were met in only 52%–72% of patients with GBS, normal CSF protein level being a main reason for not fulfilling level 1.[8,26,37] Our study has shown that CSF-TP is frequently normal in otherwise typical GBS within the first week. In the current Brighton criteria, the presence of ACD is necessary to meet level 1 criteria of diagnostic certainty. In addition, footnote 13 explains that the protein concentration may be normal in otherwise typical GBS, especially within the first week of illness. However, this covers such a large group of patients (48% at day 3) that we believe it can be justified to clarify further. Thus, we suggest emphasizing that a normal CSF-TP level in an otherwise typical GBS case may meet level 1 criteria of diagnostic certainty when LP is performed within a week from onset of symptoms. This will, however, affect the specificity of definition. The same applies for footnote 19 regarding MFS.[3]

With our findings, one might question the necessity of LP and analysis of the CSF in patients with GBS. However, these CSF characteristics at this point remain important for several reasons. First, ACD in the CSF is still the most common laboratory finding in GBS. Second, the protein level, together with clinical characteristics, may have some prognostic value in the early phase of the disease. Third, although the lack of ACD does not rule out GBS, a normal CSF examination may rule out other diagnoses with more distinct CSF characteristics, especially those with marked pleocytosis.

There are several limitations of this study. First, consistent with clinical practice, the time from onset of weakness to LP varied, complicating the interpretation of our findings. Our earlier observations showed a selection bias in the IGOS cohort toward more severely affected patients, and thus, we might have underestimated the association between CSF-TP level, disease severity, and poor outcome.[37] In addition, the proportion of patients with an elevated CSF cell count in this study may be an underestimation because clinicians may not have included these patients in IGOS until alternative diagnoses have been ruled out. Subgroup analyses on patients with ≥50 cells/μL and treatment before LP were limited by a small sample size resulting in uncertainty of the results. Further work in larger cohorts is required to validate these findings. Finally, a limitation to this study is the inability to calculate specificity and positive and negative predictive values for CSF protein levels because the IGOS database exclusively contains data on patients with GBS. Thus, future comparative studies with GBS mimics are required to determine the diagnostic value of the CSF-TP levels and may specify the consequences for the diagnostic criteria.

In conclusion, we showed that CSF-TP levels vary greatly between patients with GBS and depends on the patient's sex, timing of LP, GBS clinical variant, and NCS subtype. Lower CSF-TP level was independently associated with a better short-term outcome within the first 2–4 weeks but did not add significantly to the prediction of outcome after 4 weeks compared with previously identified prognostic factors. Last, an elevated CSF cell count ≥50 cells/μL necessitates additional investigations to rule out differential diagnoses but may be found in a small proportion of patients with otherwise typical GBS.

Author Byline *(Continued)*

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Authors, their locations, and their contributions are listed at links.lww.com/WNL/C840.

Appendix 2 Coinvestigators

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