ORIGINAL RESEARCH

CSF sphingomyelin: a new biomarker of demyelination in the diagnosis and management of CIDP and GBS

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ABSTRACT

Objective To validate sphingomyelin (SM) dosage in the cerebrospinal fluid (CSF) of patients affected by chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Guillain-Barré syndrome (GBS) as a reliably assessable biomarker.

Methods We prospectively enrolled 184 patients from six Italian referral centres, in whom CSF SM levels were quantified by a fluorescence-based assay optimised and patented in our laboratory.

Results We confirmed increased levels of SM in the CSF of patients affected by typical CIDP (n=35), atypical CIDP (n=18) and acute inflammatory demyelinating polyradiculoneuropathy, AIDP (n=12) compared with patients affected by non-demyelinating neurological diseases, used as controls (n=85) (p<0.001, p=0.0065 and p<0.0001, respectively). In patients with CIDP classified for disease stage, SM was higher in active CIDP compared with both controls and stable CIDP (p<0.0001), applying for a selective tool to treatment tailoring or withdrawal. SM was also increased in AIDP compared with axonal GBS, discrimening the demyelinating from axonal variant of the disease. SM did not correlate with CSF protein levels, stratifying patients independently from commonly used CSF indexes, and displaying high specificity to avoid potential misdiagnosis. Finally, SM correlated with the main clinical scores and some neurophysiological parameters in patients with CIDP and AIDP.

Conclusions CSF SM is a diagnostic and staging wet biomarker for acquired demyelinating neuropathies and may effectively improve the management of patients affected by GBS and CIDP.

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Guillain-Barré syndrome (GBS) are acquired immune-mediated neuropathies, characterised by strong heterogeneity in terms of clinical manifestations, prognosis and response to treatment. They are rare but treatable diseases and early recognition is essential.1 Diagnosis is based on combined clinical, laboratory and nerve conduction investigations but misdiagnosis, especially for CIDP, is very common.2

METHODS Participands and study design

We prospectively enrolled 184 neurological patients from six Italian referral centres devoted to the management of immune-mediated neuropathies. Patients were consecutively enrolled in each centre after obtaining approval from the Local Ethics Committee, starting from November 2018 and until the end of November 2019. At entry, every patient underwent a neurological examination by

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an expert group of physicians. In addition, NCS were performed in the presence of suspected neuropathy.

At the enrolment in the study and within 1 week from their admission into the hospital, all patients were subjected to spinal tap and blood withdrawal as part of the routine testing, following the consensus recommendations of the Italian Association of Neuroimmunology for immunochemical CSF examination.12

One millilitre of CSF collected for the clinical practice was immediately stored at −80°C for SM testing, to preserve lipid and protein integrity over time.13

We assigned patients to three major cohorts including definite GBS, definite CIDP and other neurological diseases (OND), used as controls, according to published criteria.9 14–16

Suspected CIDP, not fulfilling EFNS/PNS diagnostic criteria, were not included in the control group but analysed as an independent group, also referred to as ‘no EFNS/PNS CIDP’.

Inclusion/exclusion criteria, patient cohorts’ characteristics, data collection on demographical, laboratory, clinical and neurophysiological features were detailed in online supplemental information.

SM assay
SM dosage was performed by a fluorescence-based assay optimised in our laboratory (see online supplemental information for further details) (patent: 102015000078276).11

Statistical analyses
Data shown in tables were expressed as mean±SD and CI, unless otherwise specified. Results in figures 1 and 2 were presented as mean±SEM. Statistical difference between two groups was determined using the two-tailed Student’s t-test. Multiple group comparison was performed by one-way analysis of variance followed by the Holm-Sidak test. Correlation coefficient was estimated by the Spearman’s rank correlation test. We evaluated SM test performance in terms of accuracy using the receiver-operating characteristic (ROC) curve analysis. Statistical difference was considered to be significant when p<0.05. All statistical analysis was performed using the Graph Pad V.7.0 (Prism) software.

Standard protocol approvals, registrations and patient consents
Written informed consent to use CSF for SM dosage and to access to personal health information was obtained from all the patients involved in the study following the World Medical Association’s Declaration of Helsinki.

RESULTS

Patient cohorts
A total of 184 neurological patients were enrolled in the study.

Eighty-four patients were enrolled with clinical suspect of CIDP; among them, 53 fulfilled the clinical and electrodiagnostic EFNS/PNS criteria and were further divided in 35 typical (66%) and 18 atypical (34%) CIDP.14 Atypical CIDP included distal acquired demyelinating symmetric neuropathy, Lewis-Sumner syndrome, pure motor and pure sensory CIDP.15–17 Thirty-one patients among the 84 were not confirmed as definite, probable or possible CIDP. These patients were analysed as the independent group ‘no EFNS/PNS CIDP’. The group included patients finally diagnosed as neuropathy of unknown aetiology (n=11), axonal neuropathy with different comorbidities including diabetes (n=8), hereditary neuropathy with pressure palsies (HNPP) (n=2), plexopathy (n=3), multifocal motor neuropathy (n=2), anti-myelin-associated glycoprotein neuropathy (n=1), amyotrophic lateral sclerosis (n=1), deficit of vitamin B12 (n=1) and two patients with undefined diagnosis.

Fifteen patients were diagnosed as definite GBS15–16; among them, NCS allowed to identify 12 acute inflammatory demyelinating polyradiculoneuropathy (AIDP) (75%) and 3 axonal GBS (25%).

Finally, 85 patients affected by non-demyelinating neurological disorders (also referred to as OND) were used as controls. This group included patients affected by non-immune-mediated axonal neuropathy (n=19), hydrocephalus (n=9), cerebrovascular disorders (n=9), cerebral tumour (n=1), cognitive impairment (n=11), plexopathy or spondylosis (n=6), cephalgia (n=4), muscle disorders (n=3), visual impairment (n=5), cerebellar syndrome (n=3), epilepsy (n=1) and 14 healthy patients.

Relevant demographic and immunochemical data on CSF and serum are summarised in table 1.

In table 2, clinical features including disease duration and activity, response to treatment and clinical scales are listed.

Motor and sensory electrophysiological findings in patients with CIDP and GBS are reported in online supplemental tables S1 and S2. Patients with just descriptive neurophysiology (n=7) were not included in these tables. We considered demyelinating features of NCS essential to corroborate CIDP and AIDP diagnosis.17 20

Table 1 Demographic data and laboratory assessment

|                | OND (n=85) | Typical CIDP (n=35) | Atypical CIDP (n=18) | AIDP (n=12) | Axonal GBS (n=3) |
|----------------|-----------|---------------------|----------------------|-------------|------------------|
| Gender (M/F, n)| 48/37     | 27/8                | 16/2                 | 6/6         | 2/1              |
| Age (years, mean±SD) | 58±18     | 64±13*              | 68±11                | 67±11       | 74±7             |
| CSF protein (mg/L) | 0.38±0.12 (0.35–0.42) | 0.92±0.59*** (0.72–1.13) | 0.71±0.30* (0.56–0.86) | 0.68±0.31 (0.47–0.90) | 0.53±0.48 (0.19–0.88) |
| QAlb           | 6.00±3.00 (5.24–8.70) | 16.4±12.11*** (12.11–20.70) | 10.7±4.0 (8.63–12.77) | 13.0±5.76* (9.37–16.70) | 6.85±4.00 (3.75–11.00) |
| QIgG           | 3.14±1.26 (2.78–3.49) | 9.27±7.56*** (6.59–11.96) | 5.25±2.00 (4.17–6.33) | 9.00±5.55*** (5.55–12.61) | 3.14±2.40 (1.00–7.15) |
| Cells (×10³/mm³) | 1.38±0.23 (0.70–2.06) | 1.64±1.71 (1.05–2.23) | 1.22±1.07 (0.69–1.76) | 1.18±1.06 (0.50–1.86) | 0.53±0.40 (0.30–1.00) |
| OCBs CSF=S (n, %) | 20/51 (39) | 20/31 (64) | 9/14 (64) | 6/10 (60) | 2/3 (66) |

According to the literature, CIDP, independently from clinical subtype, showed a male predominance with prevalence in the elderly.17 20 The table albuminocytologic dissociation was reported for CIDP and GBS. Moreover, in up to 60% of patients with CIDP and AIDP, we found a mirror OCB pattern on isoelectric focusing (OCBs that were identical in CSF and serum; no intrathecal IgG production).

*Data were expressed as mean±SD and CI (values between parentheses), unless otherwise specified. Holm-Sidak multiple comparison test after one-way analysis of variance was used for statistical comparison of multiple groups: *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

AIDP, acute inflammatory demyelinating polyradiculoneuropathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CSF, cerebrospinal fluid; GBS, Guillain–Barré syndrome; M/F, male/female; OCB, oligoclonal band; OCBs CSF=S, oligoclonal IgG bands identical in CSF and serum; OND, other neurological diseases; QAlb, CSF to serum albumin concentration quotient; QIgG, CSF to serum IgG concentration quotient.

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**Table 2  Clinical data of patients affected by CIDP and GBS**

|                              | Typical CIDP (n=35) | Atypical CIDP (n=18) | AIDP (n=12) | Axonal GBS (n=3) |
|------------------------------|---------------------|----------------------|-------------|-----------------|
| **Disease duration (months)**| 42.0±78.0 (12.5–70.8) | 43.0±47.0 (18.2–69.1) | 0±0.3 (0.1–0.5) | 0.2±0.2 (0–0.5) |
| **Disease activity (patients in active stage/total,%)** | 26/35 (74) | 9/18 (50) | 12/12 (100) | 3/3 (100) |
| **Response to treatment (patients responding to treatment/total, %)** | 29/32 (90) | 8/11 (72) | 10/12 (83) | 2/3 (66) |
| **Clinical scales**          |                     |                      |             |                 |
| ONSLS                        | 3.7±2.2 (2.9–4.5)    | 2.4±0.9 (1.9–2.9)    | 5.9±3.0 (3.9–7.8) | 7.5±3.5 (5.0–10.0) |
| MRC sum score                | 53.9±5.6 (52.0–55.8) | 59.8±6.6 (59.4–60.1) | 44.3±11.0 (37.2–51.2) | 45.0±9.9 (38.0–52.0) |
| INCAT                        | 3.0±2.0 (2.3–3.6)    | 1.6±1.0 (1.1–2.2)    | /            | /               |
| ISS                          | 6.8±4.2 (5.3–8.3)    | 5±3 (3.4–6.5)        | /            | /               |
| GBS disability scale         | /                   | /                    | 3.2±1.0 (2.5–3.8) | 4.0±1.4 (3.0–5.0) |

Data about disease duration highlighted and confirmed the chronic phenotype of CIDP compared with AIDP. We also defined the clinical stage of the disease that was active in 100% of patients with CIDP, as expected in an acute demyelinating pathology. In typical and atypical CIDP, we estimated 74% and 50%, respectively of active patients, namely those with a clinical relapse at the moment of admission into the hospital. CIDP and GBS treatment primarily consisted of intravenous immunoglobulin and corticosteroids, less frequently plasma exchange; a large percentage of patients enrolled in the study positively responded to these treatments, displaying an improvement of at least one point in the clinical scales.

Data were expressed as mean±SD and CI (values between parentheses), unless otherwise specified.

AIDP, acute inflammatory demyelinating polyradiculoneuropathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; GBS, Guillain-Barré syndrome; INCAT, inflammatory neuropathy cause and treatment; INLS, Overall Neuropathy Limitations Scale; MRC, Medical Research Council; ONLS, Overall Neuropathy Limitations Scale.

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**SM in the CSF of patient cohorts**

We found that SM concentrations were higher in the CSF of patients affected by typical CIDP (n=35), atypical CIDP (n=18) and AIDP (n=12) compared with OND (n=85) (p<0.0001, p=0.0065 and p<0.0001, respectively) (figure 1A). These data confirmed the ability of SM testing to identify demyelination in the CSF of patients affected by acquired demyelinating neuropathies,**11** although some overlap between demyelinating neuropathies and OND could be seen.

This overlap was much less evident when SM concentrations were compared in AIDP versus axonal GBS, which showed levels similar to those of the OND, despite the low number of patients with GBS (p=0.08 and p=0.88, respectively).

Since in this study we enrolled patients with CIDP displaying clinically heterogeneous features, we decided to define different subgroups, to appreciate the relevance of SM in the complex management of the disease. First, analysing patients with CIDP grouped based on the clinical form (ie, typical and atypical CIDP), we did not find any significant difference in the CSF content of SM; instead, we detected a strong heterogeneity of SM levels within each group (figure 1A). Then, for both typical and atypical CIDP we considered the stage of the disease, thereby dividing patients in stable and active. Active CIDP was defined for those patients displaying a clinical relapse documented by the change of at least one point in the clinical scales.

Stable CIDP was defined for those patients displaying unvaried clinical scores. Based on that, we found that SM was higher in active CIDP (n=35) compared with both stable CIDP (n=18) and OND (n=85) (p<0.0001 and p<0.0001, respectively), whereas we did not observe difference between the stable CIDP and OND groups (p=0.22) (figure 1B and online supplemental figure S1A). Furthermore, while stable patients with CIDP were clinically unvaried, they displayed a residual inflammatory component that prevented their identification from the active CIDP by currently used laboratory tests, namely CSF to serum albumin concentration quotient (QAlb) (figure 1B and online supplemental figure S1B).

To further test the ability of SM to detect myelin breakdown, we also merged AIDP with the active CIDP group to form a larger cohort of patients (also referred to as active CIDP/AIDP) in which an ongoing demyelination process, at the moment of spinal tap, was deemed to be present. As expected, SM levels were higher in the CSF of these patients (n=47) compared with OND (n=85) (p<0.0001) (figure 1C).

ROC curve analysis performed on these patients' cohorts defined CSF SM levels as a very good discriminatory biomarker (area under the curve=0.9447) with an optimum cut-off of 0.9819 pmol/µL (online supplemental figure S1C). This cut-off is definitely similar to the one we calculated in our previous study (1.18 pmol/µL)11 Given that in the present multicentre prospective study a sizeable number of well-characterised patients have been investigated, we consider these results a validation of our test.

In CIDP and GBS, inflammation at the blood–spinal nerve root barrier causes a reduction of the CSF flow, and a proportional increase of the total protein content in the CSF.21 As expected, in our patients affected by CIDP and AIDP we found correlation between these indexes (online supplemental figure S2, panel A). Instead, in the same patients, SM levels did not correlate with CSF protein concentration and poorly with CSF to serum IgG concentration quotient (QIgG) and QAlb, pointing to the potentiality of SM to distinguish demyelination from inflammation (online supplemental figure S2, panel B).

Interestingly, SM concentrations were also able to recognise non-immune-mediated axonal from demyelinating neuropathy (p<0.0001), with a 100% specificity (figure 1D).

**SM and CSF protein**

In the absence of a diagnostic biomarker, increased CSF proteins remain an important supportive criterion for CIDP.7,22 However, the subjective interpretation of mild or moderate CSF albuminocytologic dissociation often contributes to misdiagnosis.1 3 22 In fact, although total protein concentration in the CSF largely depends from its levels in the bloodstream, most clinical laboratories (85%) use an upper reference limit of 0.45 g/L to consider proteins a supportive criterion for CIDP.12,23

Among patients enrolled as suspected CIDP, 31 were not confirmed.14 In these patients, namely ‘no EFNS/PNS CIDP’, compared with patients affected by definite active CIDP (n=35), CSF protein concentration displayed just a 50% specificity to correctly identify patients with CIDP (figure 2A).12 Conversely, SM dosage in the CSF of the same patients demonstrated 100% specificity to correctly recognise those affected by definite CIDP, allowing to exclude patients affected by other neuropathies...
potentially misdiagnosed as CIDP. Actually, neither of our patients, with suspected CIDP but not fulfilling EFNS/PNS published criteria, had SM levels over the cut-off (figure 2B).

**SM, clinical scores and neurophysiological parameters**

Since in this study we enrolled patients displaying clinical heterogeneous pictures, we tested whether CSF SM was sensitive enough to mirror their degree of disability. In particular, we evaluated inflammatory neuropathy cause and treatment (INCAT), Overall Neuropathy Limitations Scale (ONLS) and INCAT sensory sum score (ISS) for patients affected by CIDP; and GBS disability scale and ONLS for patients affected by GBS; to grade muscle strength we evaluated Medical Research Council (MRC) sum score for both diseases.24–31 Correlation between these scales and CSF SM content was analysed in patients affected by active CIDP (n=35) (figure 3, panel A) and AIDP (n=12) (figure 3, panel B).

Patients with CIDP displayed a low but significant correlation of CSF SM levels with the majority of clinical scales (INCAT: r=0.357, p=0.0353; ONLS: r=0.3543, p=0.0368; MRC sum
Indeed, GBS clinical scales are valid, sensitive, reliable and able for most of these patients, but there is an unmet clinical need for objective biomarkers to improve diagnosis, stage and classification of acquired demyelinating neuropathies in a clinical setting.

**DISCUSSION**

This study provides evidence that CSF SM may represent a novel diagnostic and staging biomarker, useful for the early identification and classification of acquired demyelinating neuropathies in a clinical setting.

At present, effective treatments in clinical practice are available for most of these patients, but there is an unmet clinical need for objective biomarkers to improve diagnosis, stage patients, reliably assess disease progression, as well as evaluate therapeutic interventions. To this end, demyelinating polyradiculoneuropathy is a shared pathological hallmark in patients affected by CIDP and AIDP. While several molecules reflecting tissue damaging have been suggested as biomarkers, none of them is part of the routine clinical management of these patients so far.\(^7\)\(^10\)\(^14\)

Treasuring the needs of CIDP/GBS community, we have been engaged for a few years in finding a wet biomarker that has to be endowed with clinical relevance, sensitivity and specificity, reliability, practicality and simplicity.\(^11\)

In a retrospective study performed on patients affected by CIDP and AIDP, we found that CSF SM represents a promising candidate.\(^11\)

To verify the issue, we planned the present study on a considerable number of clinically and neurophysiological well-characterised patients, prospectively enrolled. This allowed the exact classification of patients in definite subgroups corresponding to the most common variants of both CIDP and GBS, fundamental to confirm and eventually explore novel makings of SM dosage.

We confirmed the high sensitivity (80.85%) and specificity (98.82%) of SM dosage to identify patients affected by chronic and acute demyelinating polyradiculoneuropathy. In particular, we found higher levels of SM in the CSF of patients with CIDP affected by both typical and atypical form of the disease compared with controls. Among them, five patients displayed SM levels under the cut-off; interestingly, these patients had a moderate clinical impairment mainly characterised by a distal sensory involvement at the neurophysiological examination. Patients with AIDP also displayed increased CSF SM content compared with both controls and patients affected by axonal forms of GBS, although the low number of the latter ones. Overall, these results corroborated the diagnostic accuracy of SM testing.
Of note, a rapid and correct identification of demyelinating and axonal variants of GBS by CSF SM testing might help to overcome the current delay and possible misinterpretation of neurophysiology.15 35 The CSF albuminocytologic dissociation itself, that is considered a hallmark of GBS, does not discern between the different variants of the disease; in fact, rather it represents an index of inflammation and of reduced CSF flow rate and turnover caused by swellings in the area around the spinal roots.5–7 21 Instead, the SM testing, being the expression of myelin breakdown and remodelling more than of inflammation, may help to overcome the above limitation. To this end, inside the AIDP group, the two patients showing the lowest levels of SM were those enrolled in the early phase of the disease. It is likely that in these patients the inflammatory process had not yet caused substantial myelin damage.

Overall, due to these critical issues, increasing the number of patients with GBS analysed for CSF SM will be extremely important.

Concerning CIDP, we observed that clustering patients for disease activity allowed demonstrating that stable patients, independently from the clinical form and increased CSF inflammatory indexes, had SM levels comparable to those of the control cohort. Consistently, relapsing patients with CIDP showed a remarkable increase of SM in the CSF compared with both stable CIDP and controls. To this end, SM levels displayed to be more accurate than currently used CSF indexes to assign a patient with CIDP to the correct disease stage, and suggest a promising application in the evaluation of response to therapy.

Furthermore, an early and accurate diagnosis of CIDP is essential to engage a treatment and to prevent axonal damage, but is equally important to avoid severe side effects and associated costs, by prolonged therapy that needs to be stopped, when not necessary.26 36 In that sense, SM dosage may contribute to improve the pharmacovigilance of these patients.

We found that most patients with CIDP in the stable stage of the disease, based on SM levels, were treated (80%), but only 35% of them responded to therapy. Consistently, almost all patients with CIDP in the active stage displayed to be good responders to therapy (94%). SM testing facilitating the correct identification of disease stage, may therefore allow to distinguish patients who do not require further treatment either because cured, or become non-responders, from those still sensitive to therapy.

That CSF SM dosage may integrate into the management of CIDP and AIDP is further highlighted by the correlation with clinical scales, usually used to grade disease severity in these patients. Of interest, we found that this correlation was remarkable, especially in AIDP. This is expected, because of the acute nature of the disease, and the less likely existence of confounding factors in the clinical history, including disease duration, pharmacological treatment and comorbidities. Interestingly, also in patients with CIDP SM testing, although at a lower level of...
significance, correlated with clinical scores, in spite of the long-lasting disease duration and clinical heterogeneity.24

Given these promising results, SM might be envisaged as a CSF biological marker useful to corroborate ‘activity and participation level’ of CIDP and AIDP in clinical trials.24

Notably, we did not observe any correlation between CSF protein and clinical scales in both CIDP and AIDP.

Leaders within the CIDP community also raised the issue about patients misdiagnosed as CIDP. This is a crucial unexplored aspect implying medical, social and economic consequences.19 37

The large percentage of misdiagnosed CIDP is linked to a poor utilisation of clinical and electrodiagnostic criteria developed by EFNS/PNS.36–38

Equally problematic is the CSF analysis that has the potential to confuse, rather than clarify the diagnosis.5–7 23

Of note, we found that SM assay displayed a 100% specificity in the correct identification of patients affected by CIDP and exclusion of potentially misdiagnosed patients. Instead, CSF protein index displayed just a 50% specificity.22 To this end, CSF SM levels may be a more specific and informative supportive criterion than CSF protein to correctly finalise a CIDP diagnosis. Interestingly, the ‘no EFNS/PNS CIDP’ group encompassed patients affected by different types of polyneuropathy including the demyelinating inherited form HNPP; all these patients commonly might be confused for CIDP owing to misleading clinical and neurophysiological features. Actually, SM assay displayed to be able to identify them overcoming this limit. Of course, future studies involving large cohorts of patients are necessary to definitely assess CSF SM performance on the topic.

Our study has shown that CSF SM measurement can achieve a diagnosis of immune-mediated demyelinating neuropathy in more than 80% of cases tested in a specialised clinical diagnostic setting. Hundred percent of the potentially misdiagnosed CIDP, whose identification would have been extremely laborious, are correctly identified. The vast majority of patients in the active stage of the disease are properly identified; given their remarkable clinical heterogeneity, we envisage that further studies taking into account age, disease duration and the effects of immunotherapy will be able to definitely legitimise the clinical relevance of CSF SM dosage in improving the management of these patients. Furthermore, due to the typical simplicity and practicality, CSF SM dosage may be clinically acceptable from a community in which subscribing to diagnostic guidelines is still a limitation.5

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