Beyond Binary: Coexistence of Acute Motor Axonal Neuropathy and Acute Inflammatory Demyelinating Polyneuropathy in Guillain-Barré Syndrome

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Introduction

- In Guillain-Barré syndrome (GBS), complement-fixing autoantibodies target gangliosides of peripheral nerves, leading to neuroinflammation, nerve damage, and muscle weakness as primary manifestations of the disease.[1]
- Autoantibodies may target axonal tissue, resulting in acute motor axonal neuropathy (AMAN), and myelin in Schwann cells, resulting in acute inflammatory demyelinating polyneuropathy (AIDP).[2,3]
- Disease prognosis and capability of recovery vary by patient and geography, which is often attributed to GBS subtype at presentation.[1]
- However, axonal injury has been observed in both AMAN and AIDP, and this binary classification does not consider the possibility that GBS subtypes coexist.[4]
- Molecular profiling can be used to describe the underlying disease process and identify prognostic markers.[1]
- This analysis was conducted to investigate the metabolic profile of AMAN and AIDP in patients with GBS from the Phase 1 GBS-01 study.

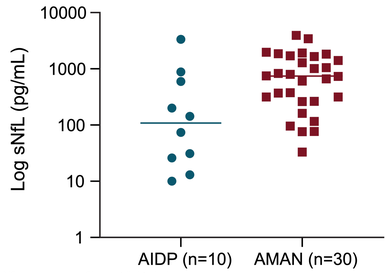
Methods

- Fifty patients enrolled in the Phase 1 GBS-01 study were included in this analysis.
- Neurofilament light chain (NfL), a marker of axonal damage, was assessed in serum only at Quanterix (Simoa platform) (sNfL, n=50), as it correlates highly with NfL levels in the cerebrospinal fluid (CSF); 10 patients were excluded because they were unresponsive/equivocal.
- CSF samples were collected at baseline and on Day 5 or 8 from 30 patients with GBS in Bangladesh with either AMAN (n=15) or AIDP (n=10) and were profiled using metabolomics (Metabolon, Inc.) and proteomics (SomaScan platform at SomaLogic); 5 patients were excluded because they were unresponsive/equivocal.
- In CSF, sphingomyelin (csfSM), a diagnostic biomarker of demyelination, and cholesterol were evaluated (n=25).
- Biomarker results were correlated with muscle strength by Medical Research Council sumscore (MRCss) and with function by GBS-disability scale (GBS-DS).
- A random forest machine learning algorithm was used to create a prognostic model on the relative importance of the association of prognostic biomarkers with the outcomes.

Results

- Baseline median sNfL was above the normal range (<9.6 pg/mL) in all patients, with higher levels in patients with AMAN (742.0 pg/mL) than in patients with AIDP (108.6 pg/mL; **Figure 1**).

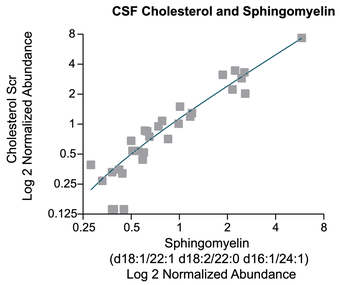
Figure 1. Median sNfL levels are elevated in AMAN and AIDP



sNfL, serum neurofilament light chain.

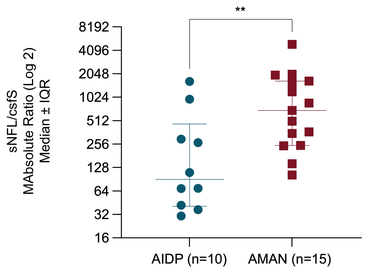
- csfSM levels were more elevated in patients with AIDP than in those with AMAN and continued to deteriorate clinically.
- csfSM correlated strongly with cholesterol levels, which were also elevated (r=0.95, p<0.0001; **Figure 2**).

Figure 2. csfSM and cholesterol levels



- The sNfL/csfSM ratio was on average 3 times higher in patients with AMAN vs patients with AIDP (p=0.010), which is consistent with the neuroimmunology of GBS (**Figure 3**).

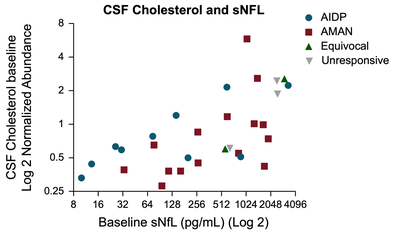
Figure 3. sNfL/csfSM ratio



**p<0.01. IQR, interquartile range.

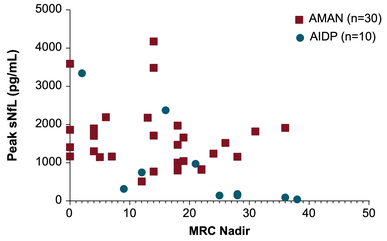
- Both NfL and cholesterol were elevated in the CSF of patients with the AMAN (Spearman r=0.55, p=0.02) and AIDP (Spearman r=0.64, p=0.03) subtypes of GBS; correlation to CSF cholesterol was non-significant in patients who were unresponsive (Spearman r=0.50, p=0.50), and there were too few pairs to draw correlations in patients who were equivocal (**Figure 4**).

Figure 4. Baseline CSF cholesterol and serum NfL correlation



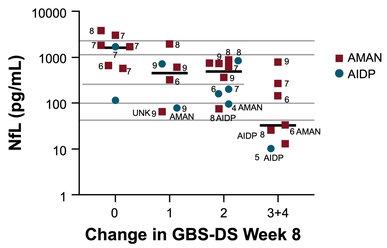
- Peak sNfL was associated with worse muscle strength (Pearson, –0.41; r2, 0.17; p=0.003; N=50) (**Figure 5**).

Figure 5. Peak serum NfL and MRC



- Patients with lower baseline sNfL were more likely to improve in function at Week 8, and this effect was consistently seen in patients with either AMAN or AIDP (**Figure 6**).

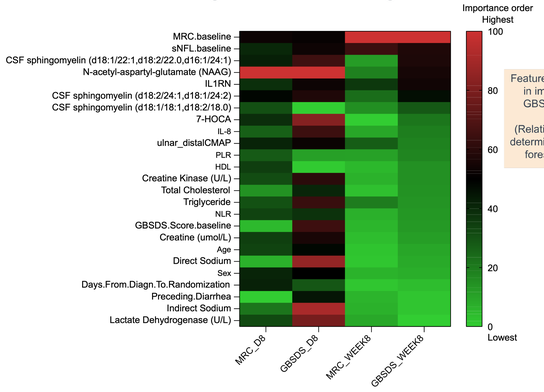
Figure 6. NfL level at Day 1 vs change in GBS-DS at Week 8



Numbers indicate days from onset of weakness.

- Independent of GBS subtype at presentation, sNfL was the most prognostic biomarker for GBS-DS at Week 8, followed by csfSM, as determined by random forest modeling (**Figure 7**).

Figure 7. Random forest modeling of biomarkers prognostic for GBS-DS at Week 8



CMAP, compound muscle action potential; HDL, high-density lipoprotein; IL-8, interleukin 8; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

CONCLUSIONS

- Patients with GBS have elevated biomarkers indicative of axonal damage and demyelination regardless of GBS subtype, suggesting that these pathological processes coexist in the presentation of GBS.
- NfL levels are prognostic for GBS outcomes regardless of variance, suggesting that the extent of axonal damage may be important for patient recovery.
- This study emphasizes the need to move beyond traditional binary neurotype classifications to explain GBS disease heterogeneity and functional outcome.

References

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