Beyond Binary: Biomarkers Reveal the Coexistence of Acute Motor Axonal Neuropathy (AMAN) and Acute Inflammatory Demyelinating Polyneuropathy (AIDP) in Guillain-Barré Syndrome

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INTRODUCTION

- In Guillain-Barré syndrome (GBS), complement-fixing autoantibodies target gangliosides of peripheral nerves, leading to 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

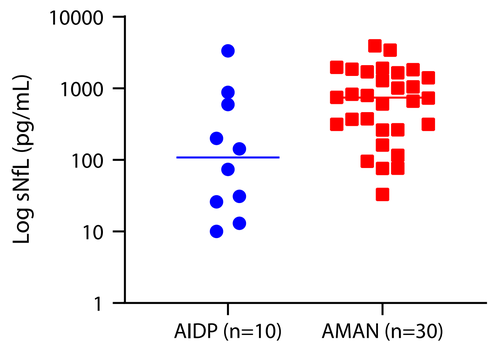
METHODS

- 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 (MRC) sum score and with function by GBS-Disability Score (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 AMAN patients (742.0 pg/mL) than AIDP patients (108.6 pg/mL, **Figure 1**)

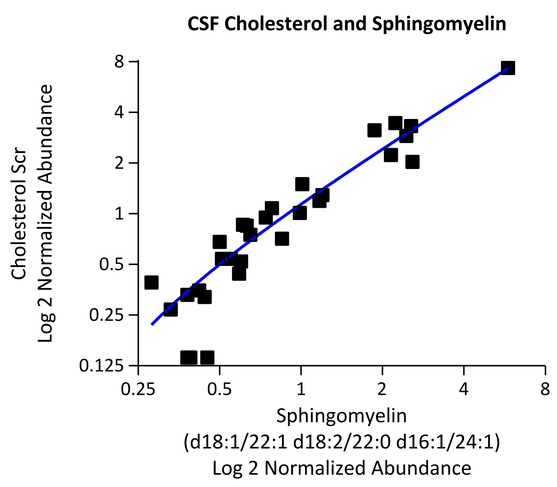
Figure 1. Median sNfL Levels Are Elevated in AMAN and AIDP



AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; 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**)

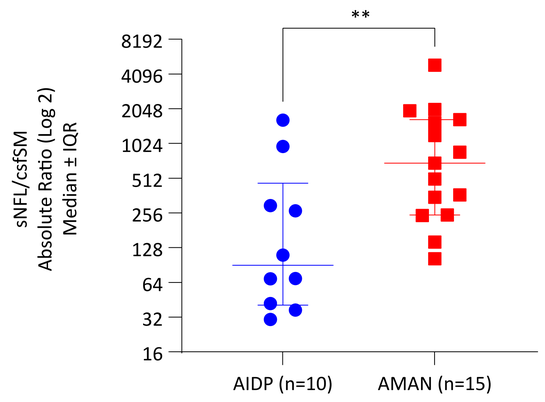
Figure 2. csfSM and Cholesterol Levels



CSF, cerebrospinal fluid.

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

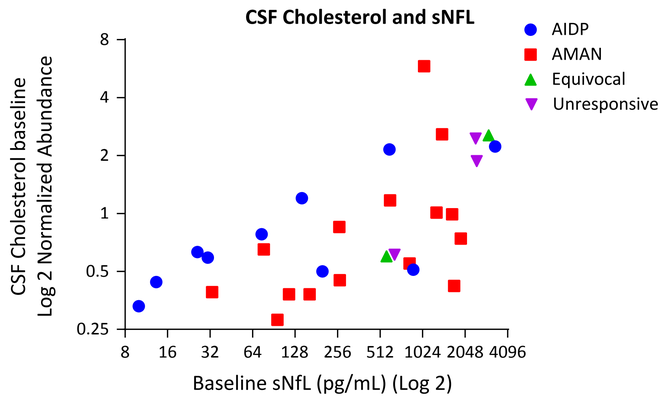
Figure 3. sNfL/csfSM Ratio



**Statistically significant.
AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CSF, cerebrospinal fluid; SM, sphingomyelin; sNfL, serum neurofilament light chain.

- 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) variants of GBS; correlation to CSF cholesterol was non-significant in patients who were unresponsive (Spearman r, 0.5; p=0.5), and there were too few pairs to draw correlations in patients who were equivocal (**Figure 4**)

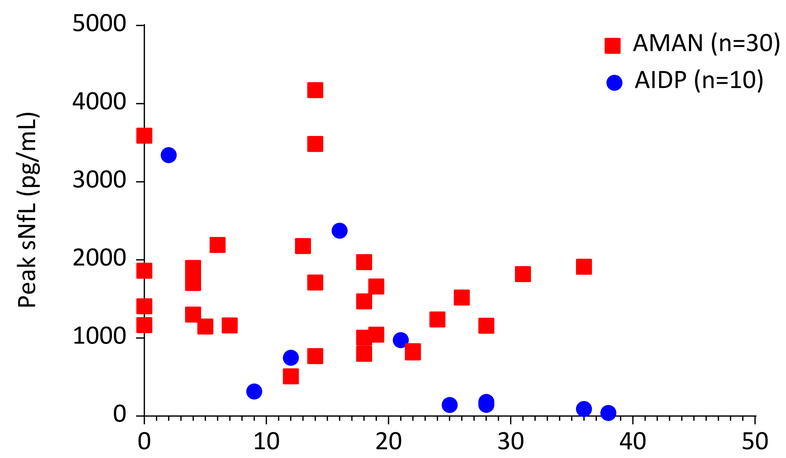
Figure 4. Baseline CSF Cholesterol and Serum NfL Correlation



AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CSF, cerebrospinal fluid; sNfL, serum neurofilament light chain.

- Peak sNfL was associated with worse muscle strength (Pearson, -0.41; r^2, 0.17; p=0.003; N=50) (**Figure 5**)

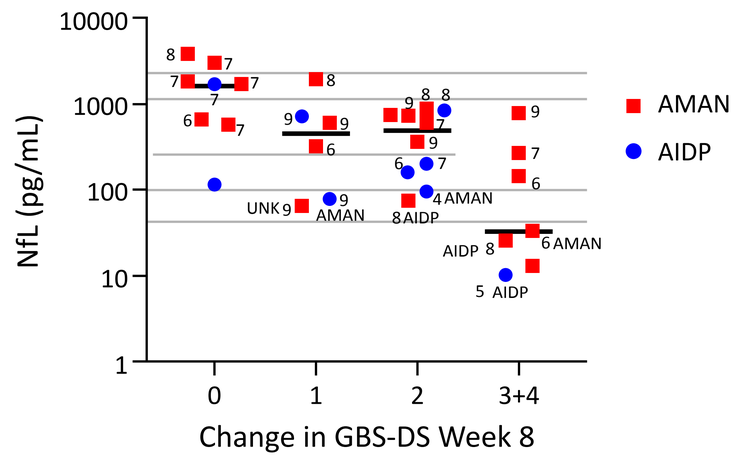
Figure 5. Peak Serum NfL and MRC



AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; MRC, medical research council sum score; NfL, neurofilament light chain.

- 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**)

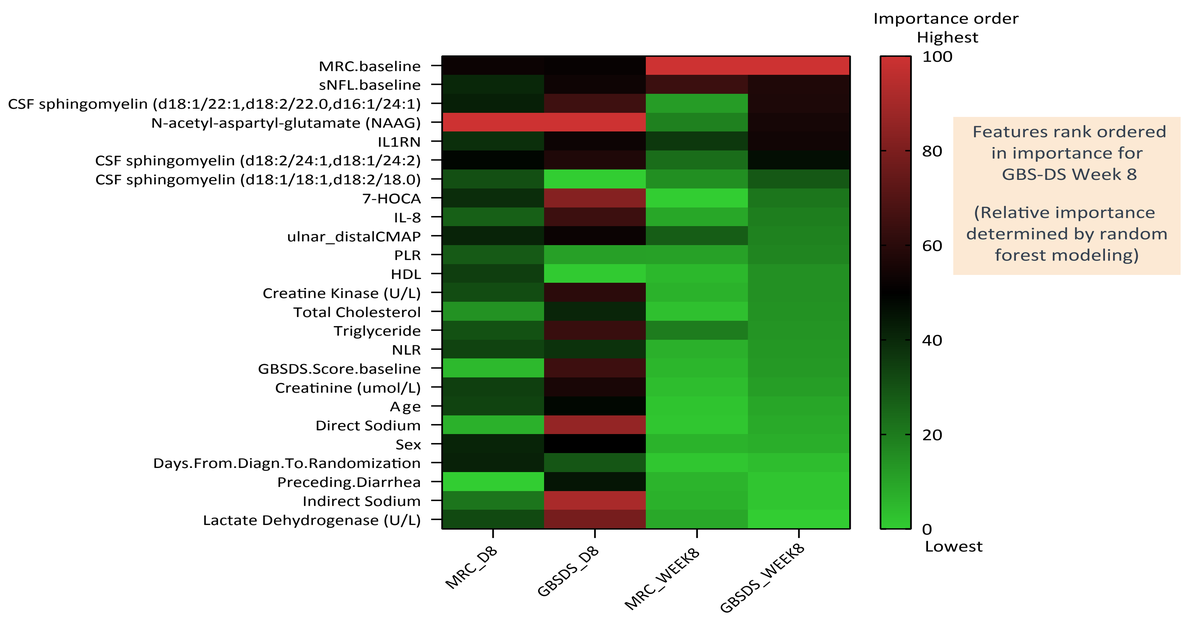
Figure 6. NfL Level at Day 1 versus Change in GBS-DS at Week 8



Numbers indicate days from onset of weakness.
AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; GBS-DS, Guillain-Barré Syndrome-Disability Score; NfL, neurofilament light chain.

- 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 modelling (**Figure 7**)

Figure 7. Random Forest Modelling of Biomarkers Prognostic for GBS-DS at Week 8



CMAP, compound muscle action potential; CSF, cerebrospinal fluid; GBS-DS, Guillain-Barré Syndrome-Disability Score; HDL, high-density lipoprotein; IL-8, interleukin 8; MRC, Medical Research Council sum score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; sNfL, serum neurofilament light chain.

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**

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DISCLOSURES

HAK, KK, EH, PP: Employment with Annexon Biosciences; equity ownership in Annexon Biosciences.
ZI: Research funding from Fogarty International Center, National Institute of Neurological Disorders and Stroke of the National Institutes of Health, and Annexon Biosciences.
QDM: Consultancy/advisory role with Annexon Biosciences.

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