Serum neurofilament light chain levels correlate with attack-related disability in neuromyelitis optica spectrum disorder

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- **B.A.C. Cree** reports personal fees for consulting from Akili, Alexion, Atara, Biogen, EMD Serono, Novartis, Sanofi and TG Therapeutics.

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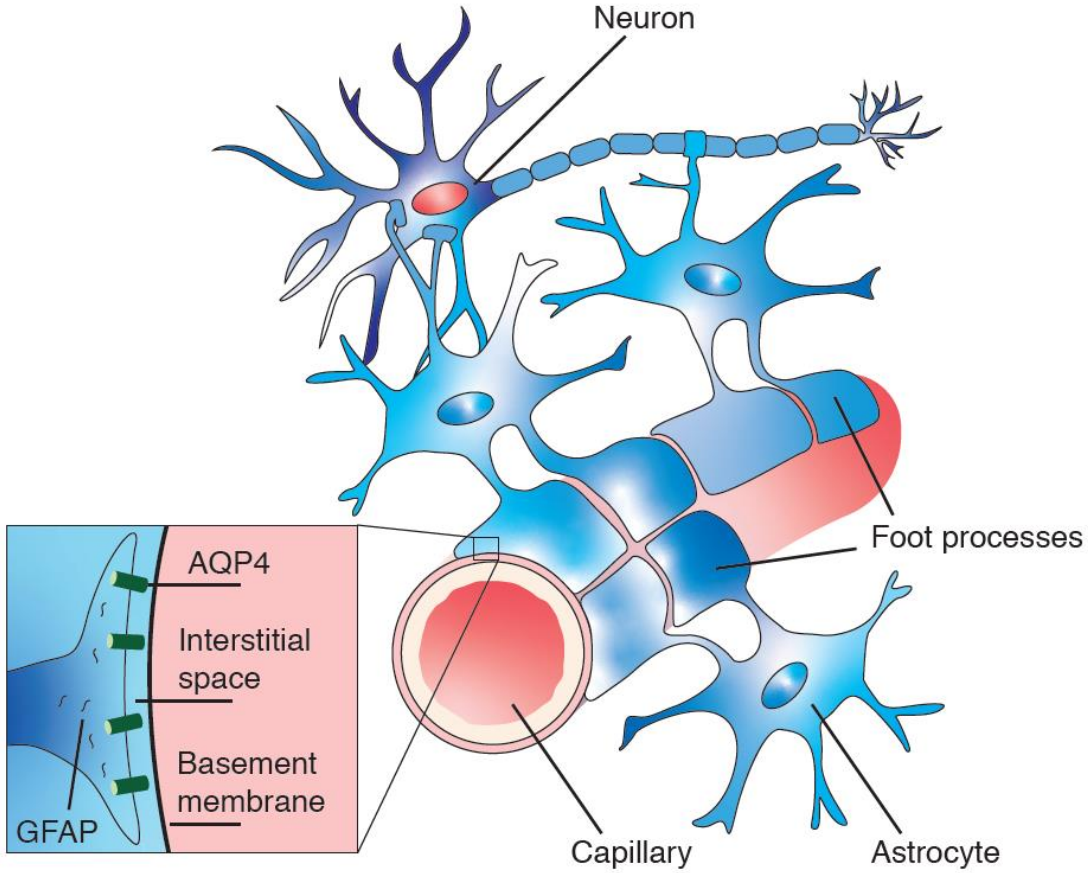
Background

- Neuromyelitis optica spectrum disorder (NMOSD) is a severe autoimmune disease, characterized by recurrent inflammation of the optic nerve, spinal cord, brain or brainstem.[1,2]
- In patients with NMOSD, aquaporin-4 (AQP-4), a water channel expressed on astrocytes, is targeted by autoantibodies, which causes the selective destruction of astrocytes and secondary neuronal damage.
- This results in the release of astroglial and neuronal proteins into the circulation such as
  - Glial fibrillary acidic protein (GFAP)
  - Neurofilament light chain (NfL)
  - Ubiquitin carboxyl-terminal hydrolase L1 (UCHL1)
  - Tau



1. Lucchinetti CF et al. Brain Pathol 2014;24:83–97.
2. Cree BAC et al. Mult Scler 2016;22:862–72.

Study design, methods and objectives

- N-MOmentum was a global, pivotal study
  - multicenter, double-blind, randomized, placebo-controlled, phase 2/3 study assessing the efficacy and safety of inebilizumab in patients with NMOSD[1]
  - Inebilizumab is a humanized monoclonal antibody with high affinity for CD19
- Serum biomarkers NfL, UCH-L1, Tau and sGFAP were measured using the single molecular array (SIMOA; Quanterix) in 1260 serial and attack-related samples from N-MOmentum participants (n=215) and healthy controls (HC; n=25).

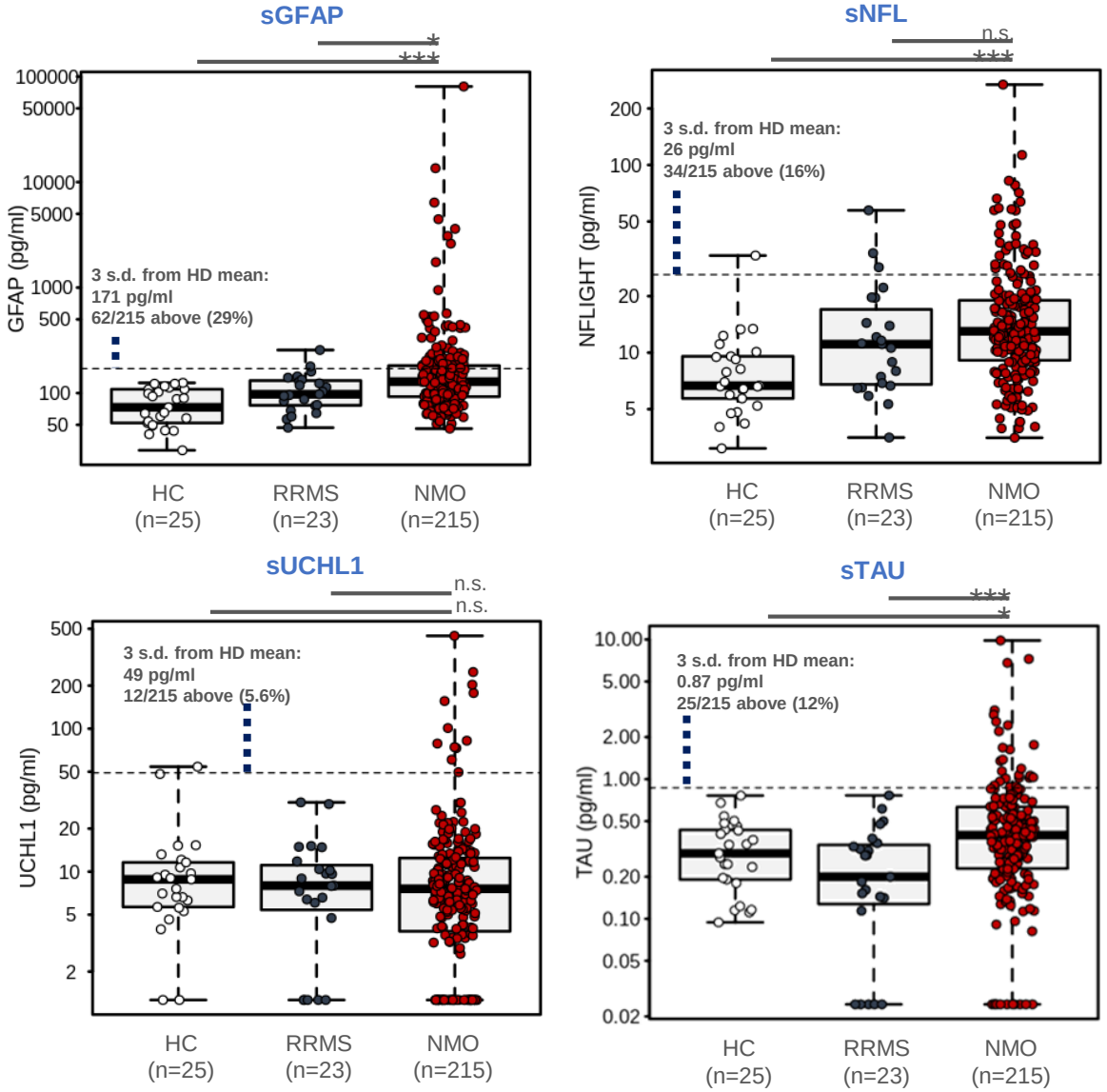
Objective:	Investigate relationships of NfL, UCH-L1, Tau and serum (s)GFAP to disease activity and Expanded Disability Status Scale (EDSS) disability in N-MOmentum trial participants with either AQP4-immunoglobulin G (IgG) seropositive or seronegative NMOSD.

NMOSD, neuromyelitis optica spectrum disorder; NfL, neurofilament light chain; sGFAP, serum glial fibrillary acidic protein; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1

1. Cree BAC, et al. The Lancet 2019, 394:1352-63

Results: Biomarkers of neuronal injury were elevated in patients with NMOSD

- Biomarker concentrations were elevated in comparison to healthy controls and patients with relapsing-remitting multiple sclerosis (RRMS)
- Statistically significant increases were noted in sGFAP (29% *p*=3.0e-07), sNFL (16%, *p*=3.4e-6) and sTau (12%, *p*=0.043) in patients with NMOSD versus healthy controls



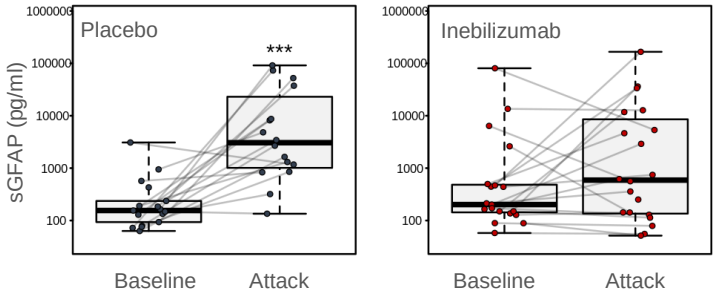
HC, healthy control; NMOSD, neuromyelitis optica spectrum disorder; sGFAP, serum glial fibrillary acidic protein; sNfL, soluble neurofilament light chain; sUCH-L1, soluble ubiquitin carboxyl-terminal hydrolase L1

1. Cree BAC, et al. The Lancet 2019, 394:1352-63

NMOSD attacks increased biomarker levels

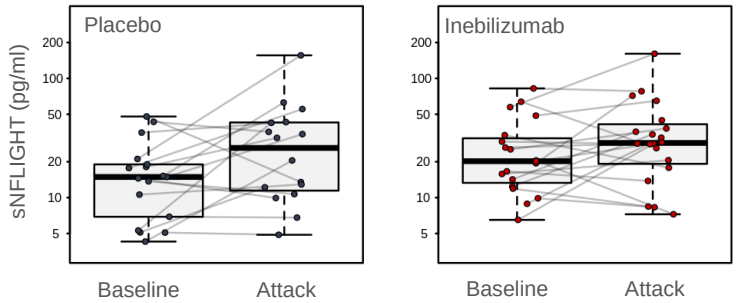
- A greater proportion of patients had an attack with placebo than inebilizumab (39% vs 12%).
- All biomarker levels increased after attacks
- Median-fold increases from baseline (95% confidence interval) trended higher with placebo than inebilizumab, reaching significance with sGFAP (p<0.05).

sGFAP vs. attack



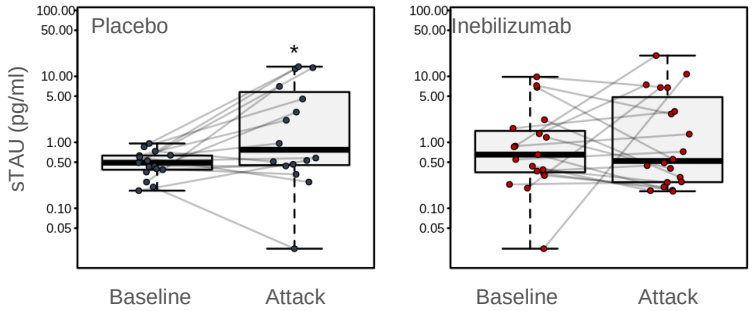
Median FC change from baseline in sGFAP:
Inebilizumab: 1.11 (0.75,24.6); Placebo: 20.2 (4.4, 98)
Mann-Whitney p-value = 0.037

sNFL vs. attack



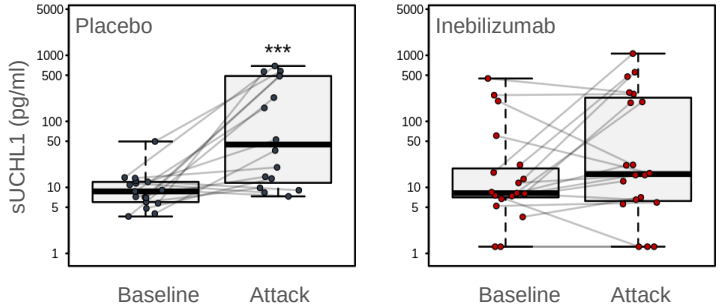
Median FC change from baseline in sNFL:
Inebilizumab: 1.30 (0.84, 2.14); Placebo: 1.49 (0.93, 3.37)
Mann-Whitney p-value = 0.40

sTAU vs. attack



Median FC change from baseline in sTAU:
Inebilizumab: 1.09 (0.40, 3.7); Placebo: 2.19 (0.96, 9.46)
Mann-Whitney p-value = 0.23

sUCHL1 vs. attack

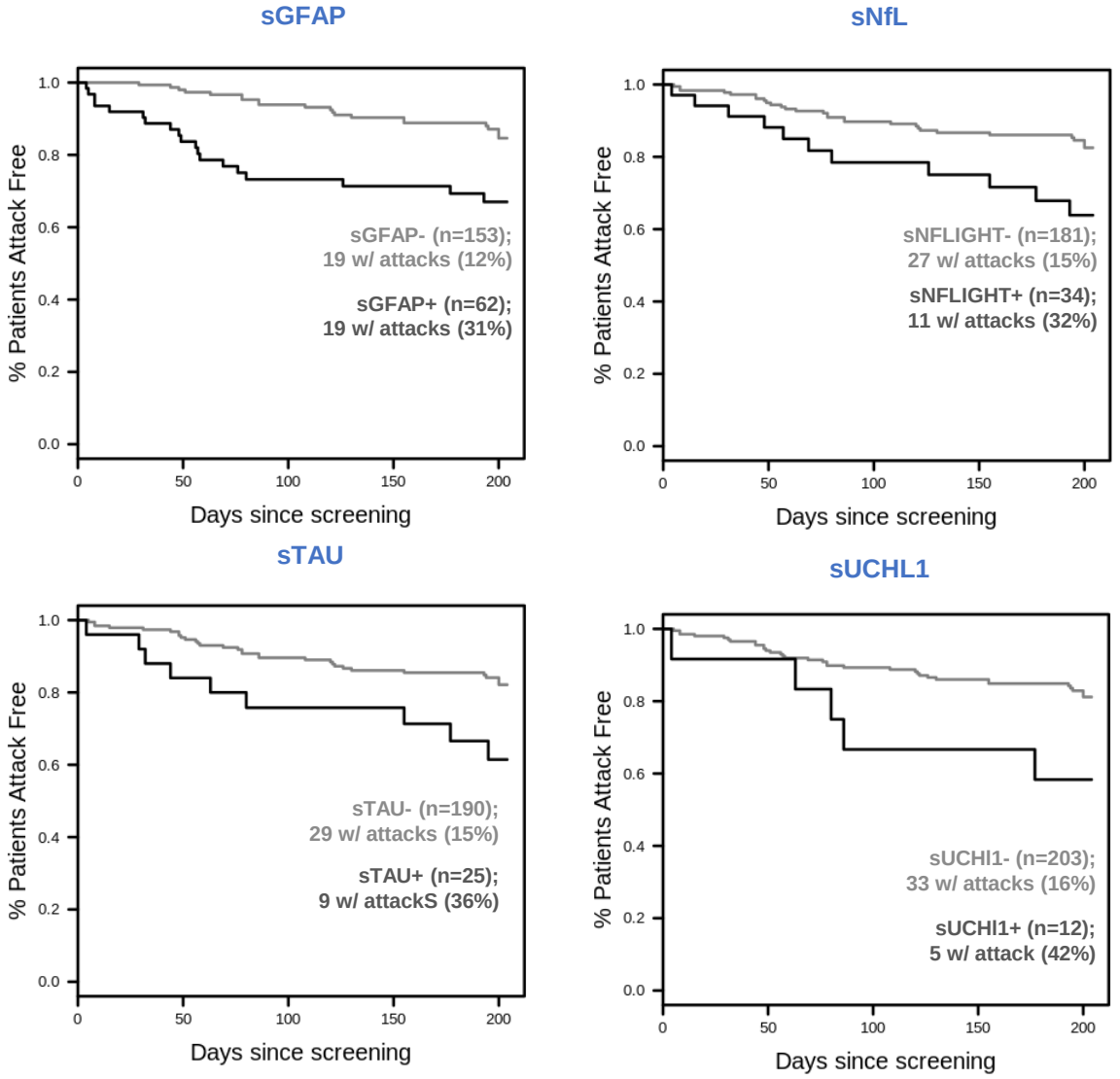


Median FC change from baseline in sUCHL1:
Inebilizumab: 1.85 (0.89, 23); Placebo: 6.70 (1.59, 52.4)
Mann-Whitney p-value = 0.12

FC, fold change; NMOSD, neuromyelitis optica spectrum disorder; sGFAP, serum glial fibrillary acidic protein; sNfL, soluble neurofilament light chain; sUCH-L1, soluble ubiquitin carboxyl-terminal hydrolase L1

Baseline elevations in biomarkers were significantly correlated with increased attack risk

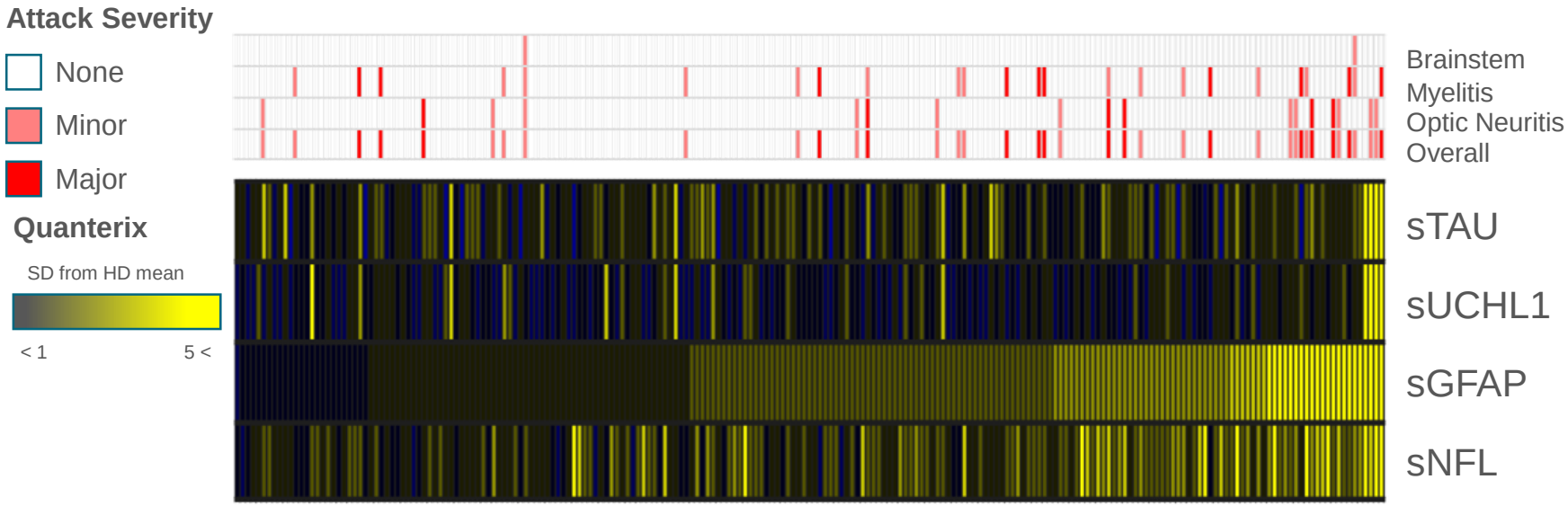
- Baseline elevations in all biomarkers assessed cause a significant increase in the risk of an attack
  - sGFAP: HR, 3.03; p<0.001
  - sNfL: HR, 2.5; p=0.01
  - sTau: HR, 2.6; p=0.01
  - sUCHL: HR, 2.8; p=0.039



HR, hazard ratio; NMOSD, neuromyelitis optica spectrum disorder; sGFAP, serum glial fibrillary acidic protein; sNfL, soluble neurofilament light chain; sUCH-L1, soluble ubiquitin carboxyl-terminal hydrolase L1

sGFAP baseline-controlled regression analysis demonstrated that biomarkers other than sGFAP were not independently associated with attack risk

- Patients with high sTAU, sUCHL1 and sNFL tended towards highest levels of sGFAP
- Cox regression analysis controlling for sGFAP concentration levels revealed that markers other than sGFAP were not independently associated with increased attack risk (hazard ratios <2, *p*>0.05)

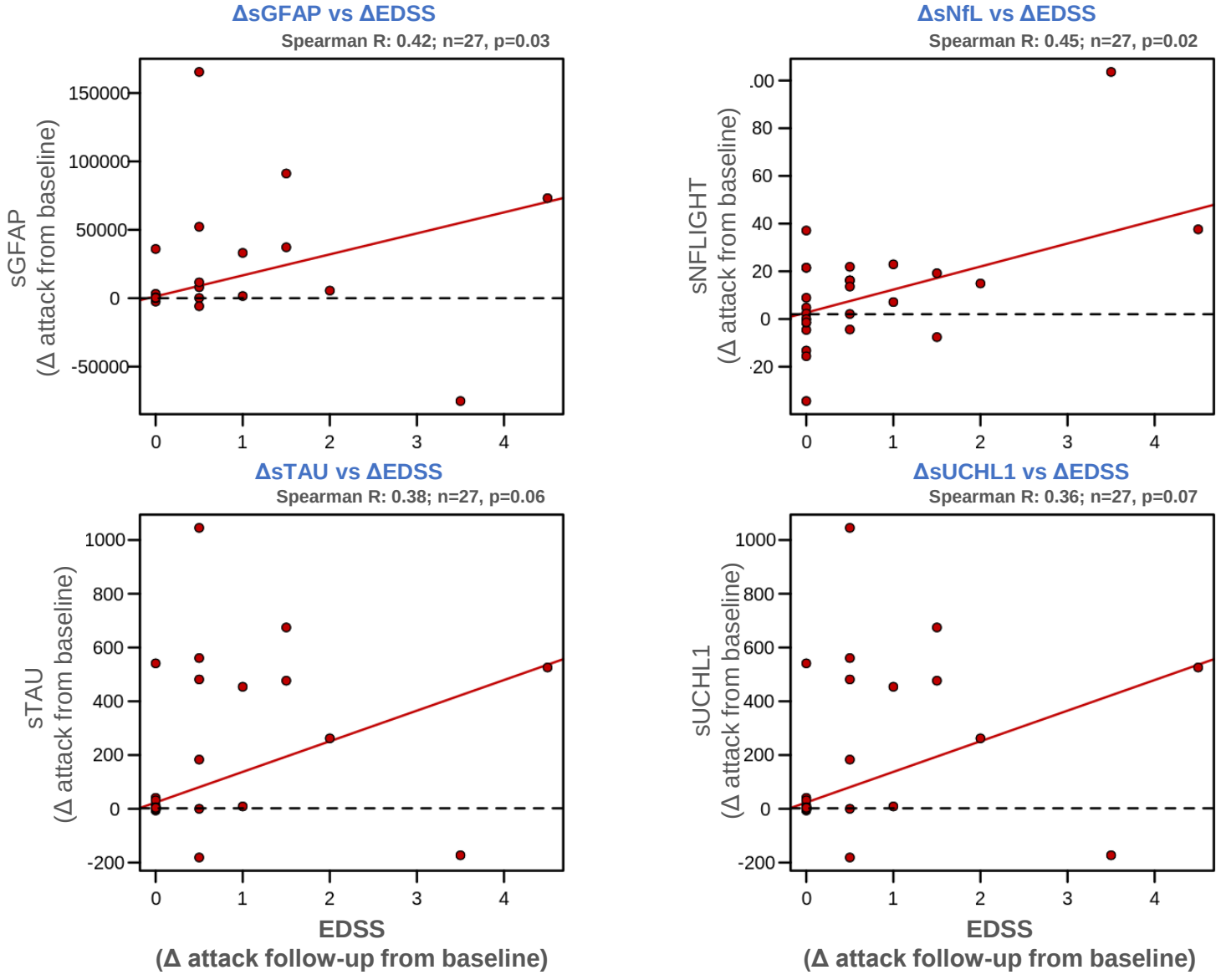


Results from multivariate cox-regression on hi/lo for 4 markers

Analyte Name	HR	p-value
sGFAP+	2.73	0.007
sNFL+	1.22	0.65
sTAU+	1.84	0.24
sUCHL1+	1.57	0.47

NMOSD, neuromyelitis optica spectrum disorder; sGFAP, serum glial fibrillary acidic protein; sNfL, soluble neurofilament light chain; sUCH-L1, soluble ubiquitin carboxyl-terminal hydrolase L1

sNFL at attack is strongest correlate of EDSS change at attack follow-up



- 4-way multiple regression on change in quanterix measurements vs change in EDSS:
  - multiple R-squared, 0.47
  - adjusted R-squared, 0.37
  - p-value, 0.008
  - T-tests on individual coefficients:

Analyte name	Estimate (±95% CI)*	p-value
sGFAP	0.00 (-0.003,0.003)	0.96
sNFL	2.9 (1.0,4.8)	0.006
sTAU	3.5 (-15.4,22.5)	0.70
sUCHL1	0.02 (-0.3,0.4)	0.89

*coefficient estimates reflect change in EDSS per 100 pg/ml change in quanterix measurement

- EDSS assessment and serum sample draw performed within 7 days of attack

Conclusions

- **Statistically significant increases were noted in sGFAP, sNFL and sTau in patients with NMOSD versus healthy controls**
- **Increased baseline sGFAP levels were associated with greater attack risk**
- **Greater increases of sGFAP were observed following attacks**
- **NfL was correlated with higher attack-related disability.**

NfL, neurofilament light chain; sGFAP, serum glial fibrillary acidic protein; sNfL, soluble neurofilament light chain.