Soluble biomarkers in MS -
Neurofilament light (NfL) and glial fibrillary acidic protein (GFAP)

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Glial fibrillary acidic protein, GFAP

- Major intermediate cytoskeletal protein of **astrocytes**
- Released into the intercellular space and CSF during astrocyte activation i.e. reactive astrogliosis (Noppe et al., 1986 Clin Chim Acta; Crols et al.,1986 J Neurol)
- Can be detected in CSF and in peripheral blood
  - Levels correlate strongly (Avsar et al., 2012 Mult Scler; Abdelhak et al., 2018 Sci Rep)
- Soluble GFAP studied mainly
  - In traumatic brain injury (TBI) (elevated in serum and CSF)
  - In stroke (elevated in serum and CSF) (Zhang et al., 2013 Neurological Sciences)
  - In AD (not altered in CSF) (Olsson et al., 2016 Lancet Neurology)
  - In PD (elevated in serum) (Su et al., 2012 Clin Neurol Neurosurg)

Literature: GFAP in **serum** in multiple sclerosis

- Serum levels were increased MS patients compared to controls (Abdelhak et al., 2018 Sci Rep, Avsar et l., 2012 Mult Scler)
  - Increase seen especially in SPMS and PPMS
- Serum GFAP levels correlated with disease severity (EDSS, MSSS, ARMSS) (Abdelhak et al., 2018 Sci Rep)
- Serum GFAP levels were not increased during MS relapses (Abdelhak et al., 2018 Sci Rep)
- Serum GFAP level was higher with increasing MRI-lesion count (>9 lesions vs. 2-9 lesions) (Abdelhak et al., 2018 Sci Rep)

Serum GFAP levels in MS- Högel et al

- At different stages of MS disease course
- In relation to serum NFL levels
- In relation to brain MRI measurements
- Collaboration with Dr. Jens Kuhle (Basel University)

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Serum glial fibrillary acidic protein correlates with multiple sclerosis disease severity

Heidi Högel, Eero Rissanen, Christian Barro, Markus Matilainen, Marjo Nylund, Jens Kuhle and Laura Airas

Multiple Sclerosis Journal

1–10

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Results: Higher serum concentrations of both GFAP and NfL were associated with higher EDSS, older age, longer disease duration, progressive disease course and MRI pathology.

Conclusion: Earlier studies have demonstrated that GFAP, unlike NFL, is not increased in association with acute focal inflammation-related nervous system damage. Our work suggests that GFAP serum level associates with disease progression in MS and could potentially serve as an easily measurable biomarker of CNS pathology related to disease progression in MS.

MSJ 2018 Högel et al

Study subjects – demographic information

- 13 healthy controls, mean age 49 years
- 79 MS patients, mean age 48 years
  - 46 RRMS
    - Mean age 46 years
    - Disease duration 11 years
    - EDSS 2.5
    - 85% immunomodulatory treatment
  - 33 SPMS
    - Mean age 56 years
    - Disease duration 21 years
    - EDSS 6
    - 40% immunomodulatory treatment

- NFL & GFAP analysis using SIMOA
- MRI imaging
  - GM, WM volumetry (Freesurfer)
  - Lesion load
  - Gd+ lesions (Freesurfer and lesion segmentation tool)

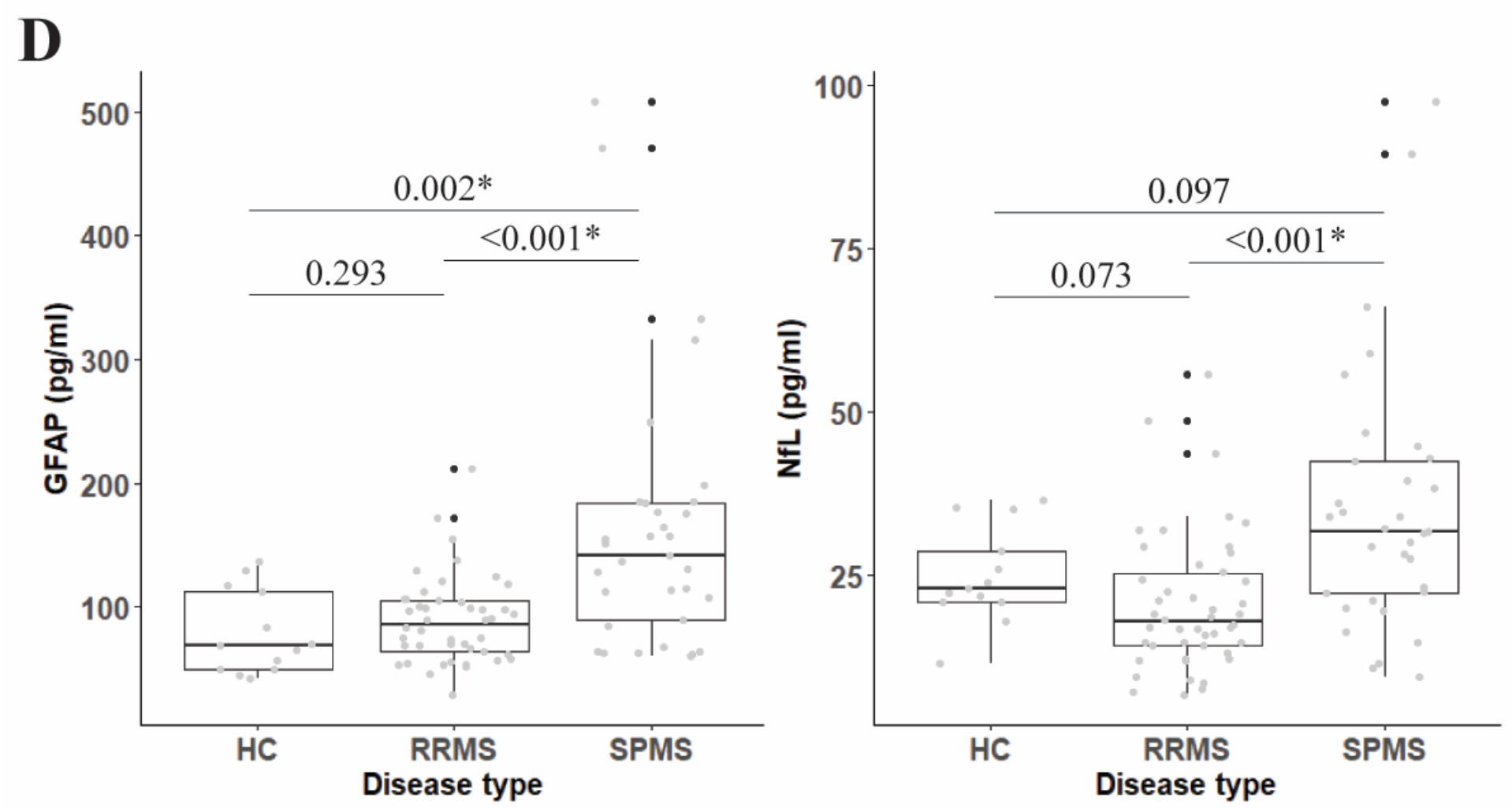
Patient cohorts - summary

- RRMS cohort low EDSS (2.5)
- Low MRI lesion load
- Low gray matter loss

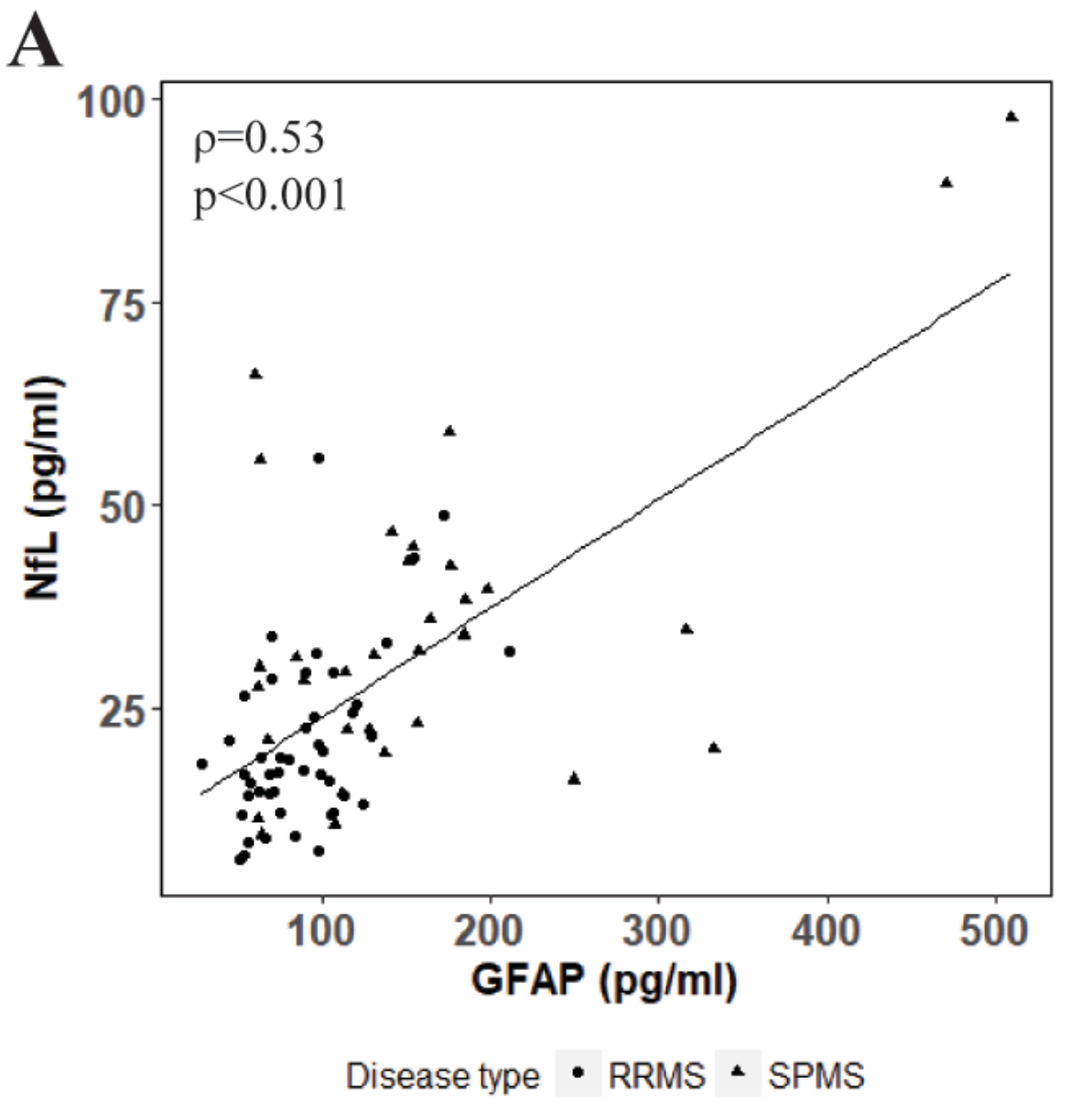
No relapses
No Gd+ lesions

- SPMS cohort high EDSS (6)
- High MRI lesion load
- Higher gray matter loss

Serum GFAP and NfL levels are higher in SPMS vs RRMS



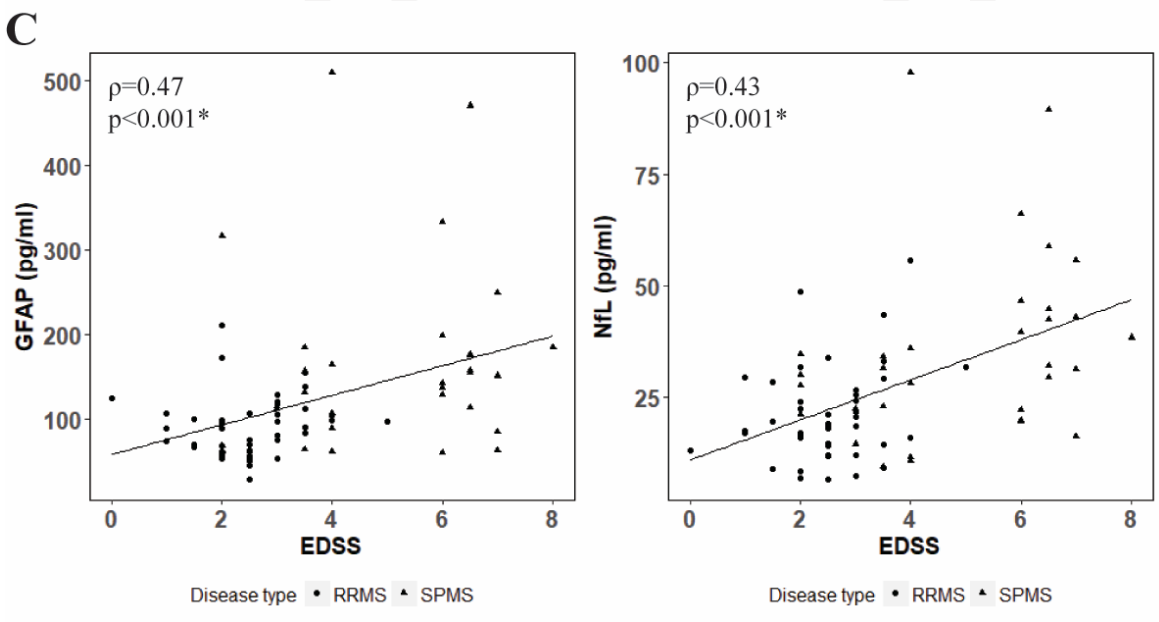
NFL correlates with GFAP



NFL and GFAP correlation with MRI and clinical parameters

- Correlation with
  - T1 and T2 lesion load
  - GM volume
- No correlation with
  - White matter volume

- Correlation with age and disease duration
- Correlation with EDSS



GFAP and NFL in MS - summary

GFAP

- CSF and serum concentrations correlate well
- CSF GFAP: no increase in acute relapses
- Serum GFAP: No increase in acute relapses
- **Serum** and CSF **GFAP: increased during progression**

NFL

- CSF and serum concentrations correlate well
- CSF NFL: Increase in acute relapses
- **Serum NFL: Increase in acute relapses**
- **Serum NFL: increased during progression**

GFAP and NFL in MS – in relation to pathogenesis

Soluble GFAP

- A marker of astrogliosis

The process of astrogliosis is significant for development of permanent CNS damage and disease progression in MS

NFL

- A marker of neural/ axonal damage

Is increased during relapse/focal inflammation.
Levels go down in 3 months after relapse.
Is associated with disease progression

Next? - Role of reactive astrocytes in MS pathogenesis

- PET imaging of reactive astrocytes

ARTICLE

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Neurotoxic reactive astrocytes are induced by activated microglia

Shane A. Liddelow[1,2], Kevin A. Guttenplan[1], Laura E. Clarke[1], Frederick C. Bennett[1,3], Christopher J. Bohlen[2], Lucas Schirmer[4,5], Mariko L. Bennett[1], Alexandra E. Münch[1], Won-Suk Chung[6], Todd C. Peterson[7], Daniel K. Wilton[8], Arnaud Frouin[8], Brooke A. Napier[9], Nikhil Panicker[10,11,12], Manoj Kumar[10,11,12], Marion S. Buckwalter[7], David H. Rowitch[13,14], Valina L. Dawson[10,11,12,15,16], Ted M. Dawson[10,11,12,16,17], Beth Stevens[8] & Ben A. Barres[1]

2017

Astrocyte function in MS pathogenesis

- A1 proinflammatory astrocytes secrete proinflammatory cytokines and cytotoxic substances
- A1 proinflammatory astrocytes promote mitochondrial dysfunction
- A1 proinflammatory astrocyte is a potent direct killer of neurons and oligodendrocytes

Use of serum soluble GFAP and NFL measurements in a clinical setting (1): Situation of **MS diagnostics**:

- Evaluation of an Individual with neurological symptoms suggestive of MS (for example paresthesia in hand)

- Brain MRI with white matter lesions
- CSF immunopathology
- **A) Both serum GFAP and NfL are increased**
  - Sign of axonal/neuronal damage (elevated NFL)
  - Sign of astrogliosis (elevated GFAP)

It is likely that chronic “neurodegenerative” pathology is already present

- **B) Only NfL is increased, GFAP is normal**
  - Sign of axonal/ neuronal damage related to relapse/focal inflammation
  - No chronic “neurodegenerative” pathology yet present

Use of serum soluble GFAP and NFL measurements in a clinical setting: **Evaluation of a potential relapse**

- RRMS patient with neurological symptoms suggestive of a relapse
- Increased serum NfL, no change in GFAP

- Sign of axonal/neuronal damage (due to acute inflammation)
- No sign of astrogliosis

- No chronic “neurodegenerative” pathology yet present

In both cases measuring only NfL would reveal only part of the picture!

Summary of our study

- Serum GFAP and NfL levels are increased in SPMS patients
- Both are lower in treated patients vs un-treated patients
- Increased levels are associated with higher lesion load and increased atrophy of cortical GM
- Levels are increased in older age and longer disease duration
- Increased serum GFAP and NfL levels are associated with higher EDSS

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