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The clinical and radiological predictive value of serum neurofilament light chain levels beyond MRI markers of lesions and atrophy in early multiple sclerosis

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Introduction

- Neurofilament light chain (NfL) is a neuron-specific protein and reflects acute neuro(axo)nal damage.
- The long-term predictive value of serum NfL in early MS and its added value beyond MRI markers remains unclear.

Objective

To evaluate the long-term clinical and radiological predictive value of serum NfL in early MS, focusing on its association with MRI-based measures of lesions and atrophy in the brain, and its predictive value beyond these MRI markers.

Methods

- Patients with early MS from the 5-year REFLEX/REFLEXION studies (NCT00404352/NCT00813709) receiving early treatment with subcutaneous interferon beta-1a (N=262) were included.
  - Demographics: 61.83% female, mean age 31.68±8.43 years, median Expanded Disability Status Scale (EDSS) 1.5 (range 0.0-4.0).

Serum and MRI markers

- Serum NfL concentrations from 6-monthly blood samples collected during the first two years.
- Age- and body mass index-corrected z-scores (based on healthy controls; zNfL) were calculated.
- For new, enlarging, disappearing, and shrinking lesions in year 1 and year 2, volumes of changing voxels were calculated using a validated semi-automated method.
- Percentage brain volume change (PBVC; global atrophy) and percentage ventricular volume change (PVVC; central atrophy) in year 1 and year 2 were calculated using FSL-SIENA/VIENA.

Disease progression

- Clinical: (time to) clinically definite MS (CDMS) and confirmed disability progression during the entire 5-year study period based on the EDSS.
- Radiological: neurodegeneration based on global and central atrophy during the last three years of the study.

Statistics

ANOVAs, correlations, and regression analyses to investigate:

- How zNfL levels evolve over time.
- The cross-sectional (baseline) and longitudinal (changes during year 1 and year 2) relationship between zNfL and MRI measures.
- How zNfL relates to the different disease progression measures.

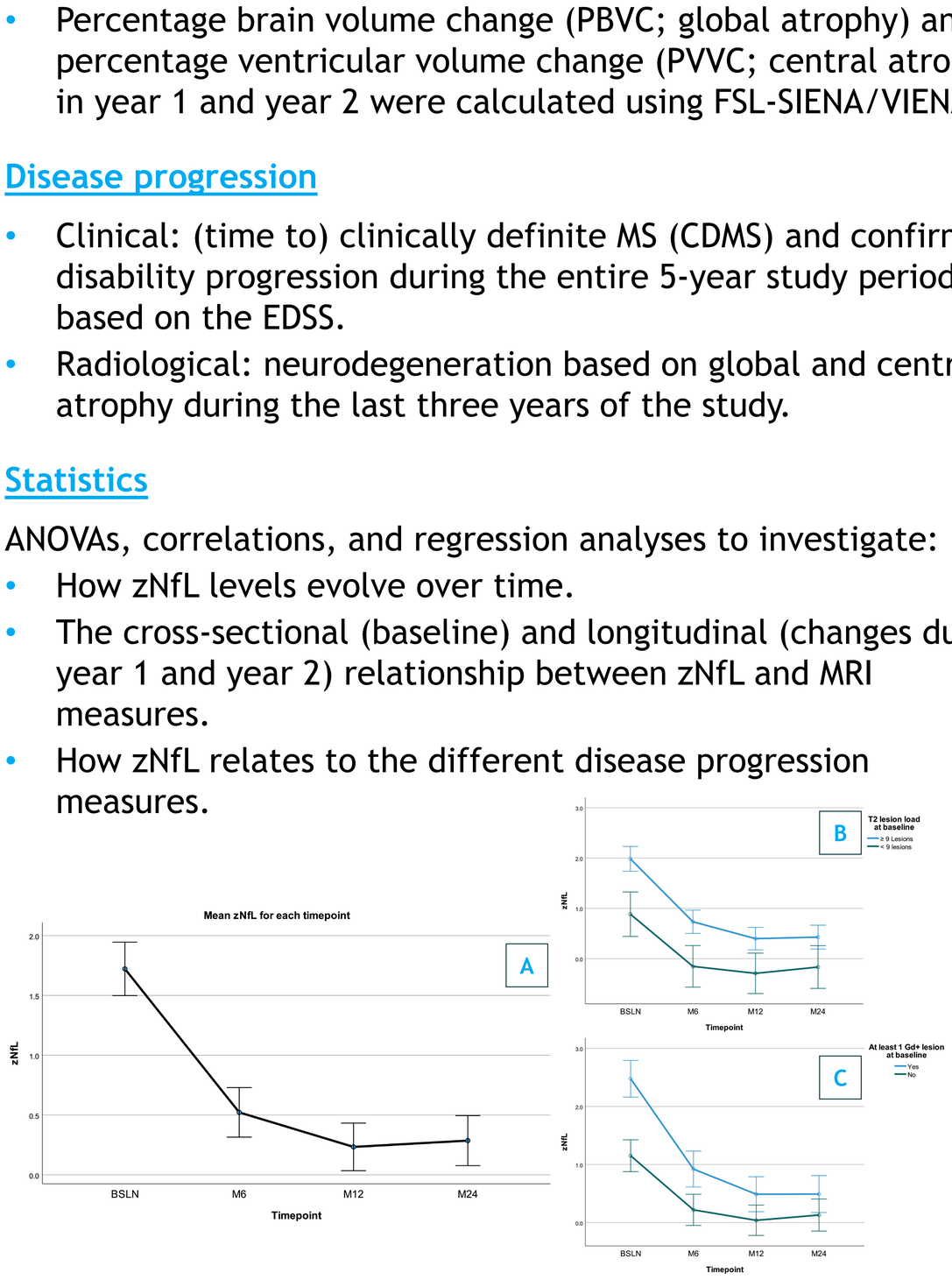

Figure 1. Mean zNfL levels (±95% confidence interval) over time (Panel A) and in different groups (Panel B and C). Panel B: subjects with less or more than nine lesions at baseline. Panel C: subjects with and without at least one gadolinium-enhancing (Gd+) lesion at baseline. BSLN = baseline, M = month.

Conclusion

- Baseline zNfL has some predictive value for disease progression, which is lost when taking MRI into account, likely due to its strong relationship with lesion activity.
- An increase in zNfL over time is linked to both less lesion shrinkage (possibly reflecting less resolution of edema) as well as more active disease and subsequent faster atrophy.

Results

Baseline zNfL

Higher baseline zNfL related to:

- Higher T2 lesion volume (Spearman's r_s=0.48, p<0.001).
- Faster central atrophy during the last three years of the study (Pearson's r=0.16, p=0.035).
- An increased risk of and faster conversion to CDMS (OR=1.18, p=0.035; HR=1.16, p=0.021).
- No longer predictive when including baseline MRI variables and demographics.

Table 1. Relationship between baseline zNfL and lesion volume changes during year 1 and year 2.

zNfL baseline	**NewLVC-y1**	**EnlLVC-y1**	**DisLVC-y1**	**ShrinkLVC-y1**
	r_s=0.33 p<0.001	r_s=0.39 p<0.001	r_s=0.34 p<0.001	r_s=0.68 p<0.001
zNfL baseline	**NewLVC-y2**	**EnlLVC-y2**	**DisLVC-y2**	**ShrinkLVC-y2**
	r_s=0.20 p=0.002	r_s=0.29 p<0.001	r_s=0.27 p<0.001	r_s=0.26 p<0.001

Dis = disappearing, Enl = enlarging, LVC = lesion volume change, y = year.

Longitudinal zNfL changes

During year 1, related to:

- Especially shrinking lesions (r_s=-0.42, p<0.001; without correction).
  - New and enlarging lesions (r_s=0.24 and 0.28, p<0.001), after correcting for baseline zNfL.

During year 2, related to:

- New and enlarging lesions (r_s=0.26 and 0.23, p<0.001).
- Global and central atrophy during the last three years of the study (r=-0.18, p=0.025; r=0.20, p=0.015; see Figure 2).
  - Also when including baseline MRI variables and demographics.

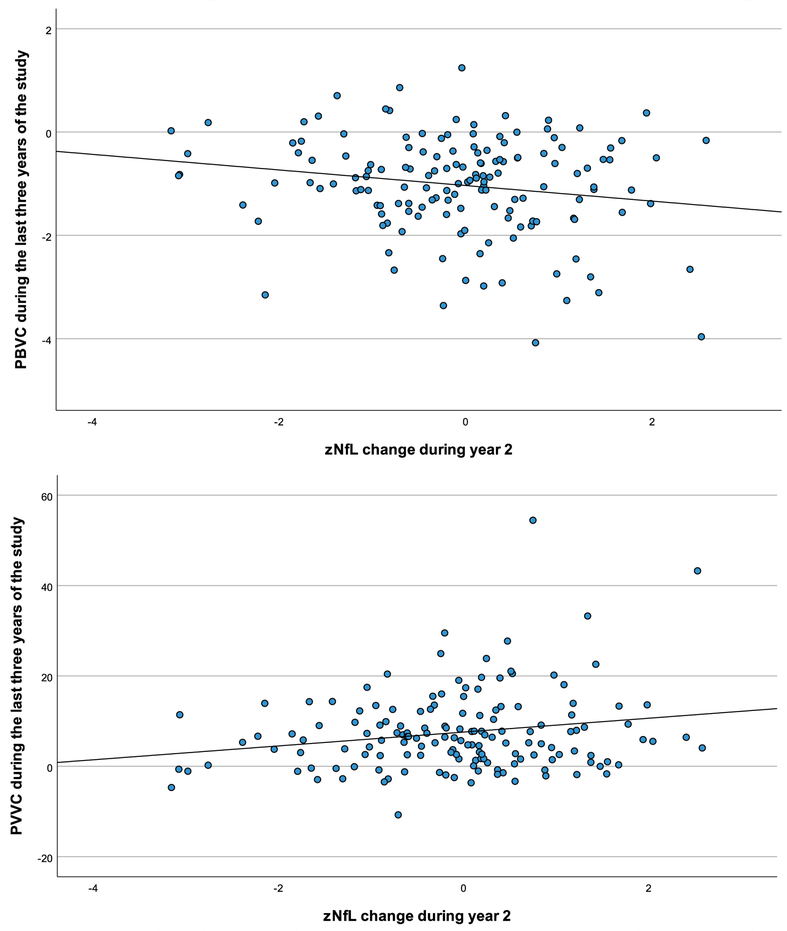

Figure 2. Scatterplots showing the relationship between zNfL change during year 2 and percentage brain volume change (PBVC; global atrophy) and percentage ventricular volume change (PVVC; central atrophy) during the last three years of the study.

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