Neurofilament light chain levels associate to white matter pathology in multiple sclerosis at clinical onset.

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Introduction. Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder affecting both white and grey matter. Biological biomarker characterizing MS disease course may help to understand the disease pathogenesis and to monitor the effect on the disease of MS therapies.

Aims. To correlate Neurofilament Ligh Chain (NfL) concentrations with MRI markers of pathology.

Materials and Methods. Paired serum and cerebrospinal fluid (CSF) were obtained from 31 patients with RRMS and 10 age and gender-matched healthy controls (HC). Routine examination of CSF and serum included Intrathecal IgG synthesis evaluation by means of quantitative formulae (IgG Index, IgG Hyp. Function for IgG intrathecal synthesis fraction (IgGIF) and Local Production (IgGLoc)) and demonstration of IgG oligoclonal bands (IgGOB). NfLs were detected in CSF by means of ELISA. MRI sequences included 3D-T1 (before and after gadolinium administration) 3D-Fluid Attenuated Inversion Recovery and 3D-Double inversion Recovery Global Cortical. Global Cortical Thickness (gCTh) were calculated on 3D-T1 sequences by means of Freesurfer. White matter lesion (volume, WMLv, and number, WMLn) and Cortical Lesion (volume, CLv, and number, CLn) were manually identified on 3D-FLAIR and on 3D-DIR respectively.

Results. RRMS patients presented more frequently IgGOB (80.6%) compared to HC (0%, $p<0.001$), but intrathecal IgG synthesis parameters and CSF-NfL concentrations did not differ between the two groups. While CSF-NfL concentrations correlated with QAlb (0.81, $p<0.01$) in HC, even when excluding the higher CSF-NfLvalue (r:0.66, $p<0.05$), in RRMS this correlation was slightly reduced but sill significant (r:0.41, $p<0.05$)(Figure 1). Moreover, in RRMS CSF-NfL correlated with WMLn (r:0.62, $p<0.001$), WMLv (r:0.48, $p<0.01$) and CLn (0.56, $p<0.005$), but not with CLv (r:0.15, p=0.44). However, when excluding the higher CSF-NfL value, only the correlation between WMLV and CSF-NfL was confirmed (r:0.48, $p<0.01$). Applying a multivariate analysis considering NfL as dependent variable, both QAlb and WMLn were strongly associated in RRMS (r^2.0.65, $p<0.001$) (Table 1).
When dividing SMRR patients based on CSF-NfL (higher concentrations, NfLhigh; lower concentrations, NfLlow), NfLhigh had higher WMLv (4439.8±4640.2 mm^3) and CLv (102.9±121.8 mm^3) compared to NfLlow (1059.8±830.6 mm^3, 33.3±35.0 mm^3 respectively both $p<0.05$).

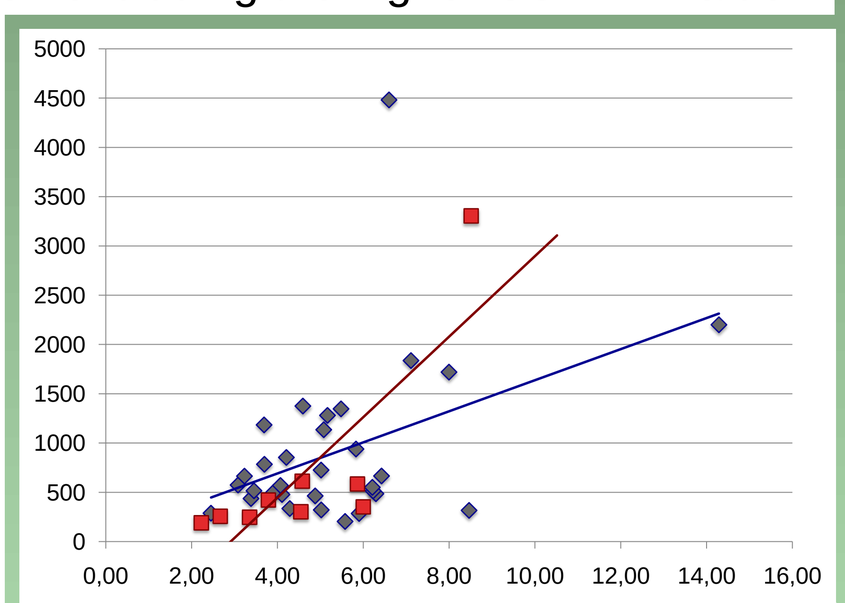

Figure 1. The correlation between Qalb and CSF-NfL was stronger in HC than in RRMS. However, multiple linear regression analysis did not disclose any difference within HC and RRMS.

	Beta	p-value
Q_{alb}	*3.70*	*<0.005*
WMLn	*3.47*	*<0.005*
GMLn	*2.40*	*<0.05*

Table 1. Multiple linear regression analysis. CSF-NfL concentrations in RRMS were strongly associated with Qalb, WMLV and GMLV. These 3 variables were able to explain 65.1% of the CSF-NfL variability in MS patients

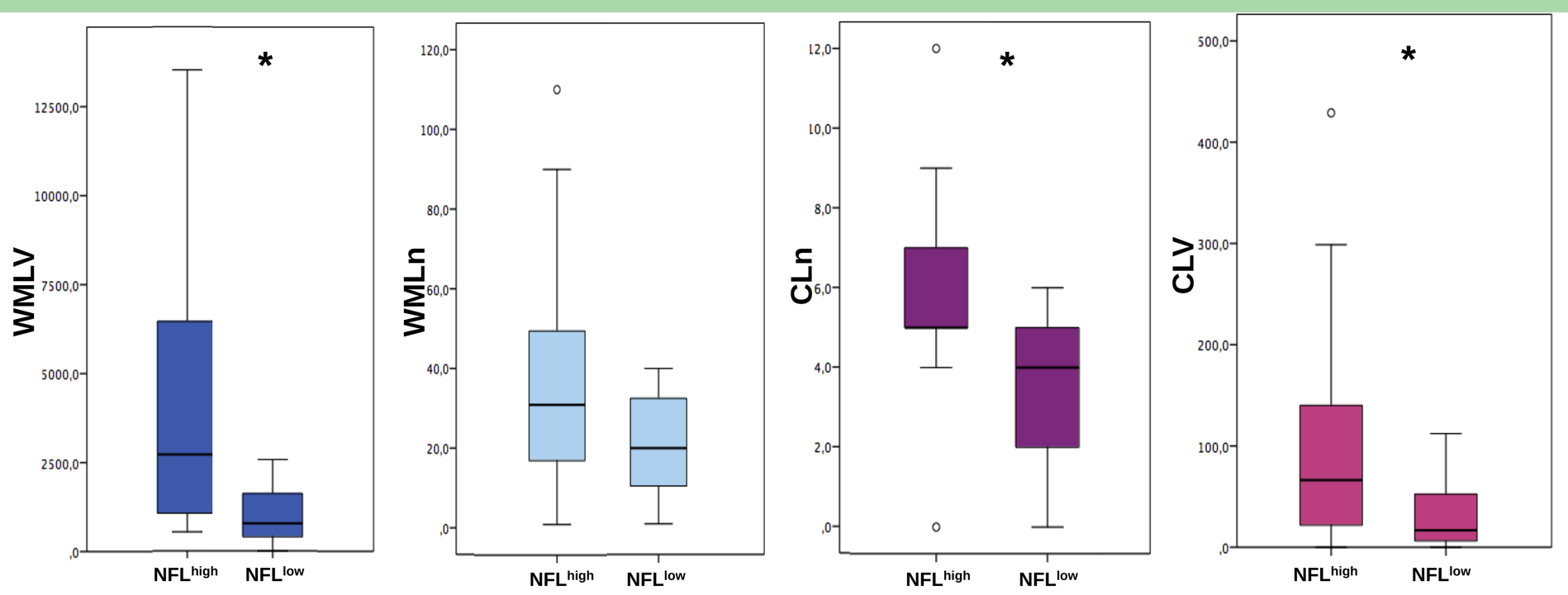

Figure 2. Both grey and white matter lesions were increased in MS patients with higher concentrations of NFL in the CSF. Only WMLn was not significantly higher in NFL^{high} patients.
Abbreviations: NFL^{high}: MS patients with NFL concentration higher than the median; NFL^{low}: MS patients with NFL concentration lower than the median; WMLV: white matter lesion volume; WMLn: white matter lesion number; CLV: cortical lesion volume; CLn: cortical lesion number.
*:$p<0.05$

Finally, CSF-NfL did not correlate with gCTh in HC, RRMS, NFLlow and NFLhigh .

Conclusions. Reflecting white matter inflammation, NfLs should be considered as a promising biomarkers in MS. The mild correlation with CLn and the lack of correlation with gCTh question NfL as marker of cortical pathology.

Puthenparampil Marco received travel grant from Novartis, Genzyme, Biogen Idec, Teva and Sanofi Aventis; he has been consultant for Genzyme. Zywicki Sofia and Lazzarotto Andrea have nothing to disclose. Federle Lisa has received funding for travel from Novartis, Merck Serono, Biogen Idec, Sanofi-Aventis, Bayer Schering Pharma, Almirall, Genzyme, Teva and honoraria from MerkSerono, Teva and Almirall. Rinaldi Francesca serves as an advisory board member of Biogen-Idec and has received funding for travel and speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, Teva, Novartis and Genzyme Sanofi and Bayer Schering Pharma. Perini Paola has received funding for travel and speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, and Bayer Schering Pharma and has been consultant for Merck Serono, Biogen Idec and Teva. Gallo Paolo has been a consultant for Bayer Schering, Biogen Idec, Genzyme, Merck Serono and Novartis; has received funding for travel and speaker honoraria from Merck-Serono, Biogen Idec, Sanofi-Aventis, Novartis Pharma and Bayer-Schering Pharma, Teva; has received research support from Bayer, Biogen Idec/Elan, MerkSerono, Genzyme and Teva; and has received research grant from the University of Padova, Veneto Region of Italy, the Italian Association for Multiple Sclerosis, the Italian Ministry of Public Health.