nature reviews neurology

https://doi.org/10.1038/s41582-024-00955-x

Review article

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Neurofilaments as biomarkers in neurological disorders — towards clinical application

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Supplementary Table 1 | Key studies supporting the clinical use of neurofilaments in MS, NMOSD and MOGAD

Study	Study design and data analysis	Target, sample type (assay used)	Participants	Association with clinical and imaging metrics, disease activity and/or progression	Key conclusion(s)
Lycke 1998[1]	RCT (acyclovir versus placebo), cross-sectional, observational	NfL, CSF (ELISA Rosengren, 1996)[2]	60 RRMS, 11 HC	NfL associated with relapse rate and EDSS; levels increased for at least 5 months after relapse. NfL levels higher in people with RRMS than in HC. No influence of acyclovir on NfL levels.	Early evidence of higher NfL in people with RRMS than in HC.
Petzold 2005[3]	Cross-sectional and longitudinal, observational	NfH, CSF (ELISA Petzold 2003)[4]	34 MS (RRMS, SPMS, PPMS) 318 controls	NfH correlated with all clinical scales at baseline at follow-up. NfH higher in SPMS and PPMS than in RRMS at baseline and follow-up.	High NfH levels are a poor prognostic sign in MS.
Brettschneider 2006[5]	Cross-sectional and longitudinal, observational	NfH, CSF (ELISA Petzold 2003)[4]	52 CIS, 38 RRMS, 25 controls	NfH higher in CIS compared with controls; NfH higher in RRMS with acute relapse than in stable RRMS. NfH levels correlated with EDSS in CIS and RRMS. NfH predicted conversion from CIS to MS with a higher sensitivity and specificity than MRI.	Predicting conversion from CIS to MS can be improved if CSF markers are combined with MRI.
Gunnarsson 2011[6]	Longitudinal, observational	NfL, CSF (ELISA Uman Diagnostics)	83 RRMS, 9 SPMS, 28 HC	NfL higher in participants with MS during relapse (within 3 months) than in remission. NfL levels reduced after natalizumab treatment (independent of relapse).	This study indicated the potential of NfL as a treatment outcome parameter.
Disanto 2017[7]	Cross-sectional, observational	NfL, CSF, serum (Simoa)	48 CIS, 62 RRMS, 3 SPMS, 16 PPMS, 13 RIS	Increased serum levels of NfL in patients withCEL or a higher MRI lesion load.	This study provided substantial evidence for the ability of the Simoa assays to reflect clinical and imaging activity in MS.
	Longitudinal, observational	NfL, serum (Simoa)	14 CIS 185 RRMS, 27 SPMS, 20 PPMS, 254 HC	Serum NfL levels were higher during relapses and were associated with higher EDSS. Lower levels following initiation of highly effective treatments.	
Barro 2018[8]	Cross-sectional and longitudinal, observational	NfL, serum (Simoa)	11 CIS, 178 RRMS, 54 SPMS, 14 PPMS, 259 HC	NfL higher in all forms of MS compared with HC. Elevated NfL in people with CEL. Elevated NfL values compared with HC was independent predictor of EDSS worsening and faster rate of brain atrophy.	NfL reflects neuro-axonal damage outside of routine MRI measures.
Sormani 2019[9]	Phase III RCT (fingolimod vs placebo), longitudinal	NfL, Serum (Simoa)	246 RRMS	In treated participants, NfL levels correlated with number of relapses and CEL. NfL levels associated with 6-month confirmed disability worsening.	Blood NfL may qualify as an informative and easy-to-measure endpoint for future phase II clinical studies that captures both inflammatory and degenerative neuro-axonal injury in RRMS.

Benkert 2022[10]	Longitudinal, observational	NfL, serum, plasma (Simoa)	1313 RMS, 5390 HC	Association of NfL Z-scores with future acute disease activity. Association of longitudinal change of NfL with clinical efficacy of DMT.	Established normal values corrected for age and BMI, based on Z-scores/percentiles, accessible as reference data base via internet (https://shiny.dkfbasel.ch/baselnflreference/).
Meier 2023[11]	Cross-sectional, and longitudinal observational	NfL, serum (Simoa)	355 MS, 295 HC	People with MS with disease progression had 50.9% higher GFAP levels compared with those with stable MS independent of serum NfL, whereas the 25% increase of NfL was not independent of serum GFAP concentration. The combined elevation of Z-scores of NfL and GFAP had the best predictive capacity for disease progression.	NfL captures acute disease activity in MS, whereas GFAP was superior for capturing disease progression. Combining NfL with GFAP might improve disease progression prediction models in MS.
Abdelhak 2023[12]	longitudinal observational	NfL, serum (Simoa)	1899 MS (609 EPIC and 1290 SMSC)	NfL Z-scores were higher in people with CDW ~ 12 months preceding CDW with relapses, and 1–2 years preceding CDW independent of relapses. Time-to-event analysis confirmed the association between NfL levels and future CDW in the corresponding time windows.	This work substantiates the association and predictive value of NfL related to CDW and hint to a potential window of ongoing CNS pathology that precedes the diagnosis of CDW.
Miyazawa 2007[13]	Cross-sectional, observational	NfH, CSF (ELISA)[14]	24 MS, 24 NMO, 4 relapsing myelitis	NfH levels were higher in NMO vs MS and relapsing myelitis.	This study suggested more severe neuro-axonal damage in NMO thank in MS.
Watanabe 2019[15]	Cross-sectional, observational	NfL, CSF, serum (Simoa)	43 NMOSD, 43 MS, 49 HC	Serum levels of NfL and GFAP higher in NMOSD vs MS. Higher GFAP/NfL quotient at relapse differentiated NMOSD from MS with a sensitivity of 73.0% and a specificity of 75.8%.	The findings of this study substantiated the evidence for more severe neuro-axonal and glial injury in MNOSD vs MS.
Mariotto 2019[16]	Cross-sectional, observational	NfL, CSF, serum (Simoa)	38 MOGAD 38 HC	CSF and serum NfL levels were correlated, increased in MOGAD vs controls, are correlated with attack severity, and tend to correlate with long-term disability.	Serum NfL is an adequate measure of attack severity in MOGAD.

CEL, contrast enhancing lesions; CIS, clinically isolated syndrome; CSF, cerebrospinal fluid; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; ELISA, enzyme-linked immunosorbent assay; EPIC, The Expression, Proteomics, Imaging, Clinical (EPIC) study at the University of California San Francisco; GFAP, glial fibrillary acidic protein; HC, healthy controls; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NfH, neurofilament heavy chain; NfL, neurofilament light chain; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; PPMS, primary progressive multiple sclerosis; RCT, randomized controlled trial; RIS, radiologically isolated syndrome; RMS, relapsing multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SMSC, Swiss Multiple Sclerosis Cohort; Simoa, single-molecule array; SPMS, secondary progressive multiple sclerosis.

Supplementary Table 2 | Key studies supporting the clinical use of neurofilaments in neurodegenerative dementias.

Study	Study design and data analysis	Target, sample type (assay used)	Participants	Diagnostic and/or prognostic relevance
Pijnenburg 2015[17]	Cross-sectional	NfL, CSF (ELISA Uman diagnostics)	15 FTLD–TDP with ALS, 17 FTLD–TDP without ALS, 6 FTLD–Tau, 25 Alzheimer's disease, 24 SMC	FTLD–TDP (with and without ALS) vs AD and SMC: AUC 0.99
Steinacker 2016[18]	Cross-sectional	NfL, CSF, serum (Simoa)	99 genetic and sporadic CJD, 60 controls	CJD vs controls: CSF: sensitivity 97.3%, Specificity: 86.5%. Serum: sensitivity 100%, specificity 85.5%
Steinacker 2017[19]	Cross-sectional	NfL, serum (ECL)	40 nfvPPA, 38 svPPA, 21 lvPPA, 45 HC	All PPA vs HC: 95% sensitivity and 70% specificity; nfvPPA/svPPA vs lvPPA: 81% sensitivity and 67% specificity.
Byrne 2017[20]	Longitudinal	NfL, plasma (Simoa)	201 individuals carrying HTT, 97 controls	Mean concentrations of NfL in plasma at baseline were significantly higher in *HTT* mutation carriers than in controls
Bridel 2019[21]	Individual level data meta-analysis. Cross-sectional data points.	NfL, CSF (ELISA Uman diagnostics)	2,795 neuroinflammatory disorders, 4,284 dementias and pre-dementia stages, 984 parkinsonian disorders, 1,332 HC	CSF NfL increased in the majority of patients. NfL levels were similar among neurological diseases. Exception was the increase in FTD compared to other dementias. Increase in atypical parkinsonian disorders vs PD. Strong NfL elevation was also observed for HD, ALS and dementia due to HIV.
Ashton 2021[22]	Cross-sectional	NfL, plasma (Simoa)	2,265 patients with neurodegenerative disorders, including FTD, PDD, CBS, AD, ALS	Age >65 years: all neurodegenerative disorders vs controls, AUC 0.829. AUC worse (0.74) if PD included. Age >65 years: all neurodegenerative disorders vs controls, AUC 0.90. AUC worse (0.75) if PD included.

AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; AUC, area under the curve; CBS, corticobasal syndrome; CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; ECL, electrochemiluminescence; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; FTLD–TDP, frontotemporal lobar degeneration with TDP pathology; FTLD–tau, frontotemporal lobar degeneration with tau pathology; HC, healthy controls; lvPPA, logopenic variant primary progressive aphasia; NfL, neurofilament light chain; nfvPPA, nonfluent variant primary progressive aphasia; PD, Parkinson disease; PDD, Parkinson disease dementia; PPA, primary progressive aphasia; SMC, subjective memory complaints; svPPA, semantic variant primary progressive aphasia.

Supplementary Table 3 | Key studies supporting the clinical use of CSF and blood neurofilaments in ALS.

Study	Study design and data analysis	Sample type, assay used	Participants	Association with disease severity and biomarker dynamic	Diagnostic and/or prognostic relevance	Relevance as drug response marker
Brettschneider 2006[23]	Cross-sectional and longitudinal, observational	NfH, CSF (ELISA Petzold 2003)[4]	69 ALS, 73 AD, 33 controls	NfH higher in upper motor neuron-dominant ALS than in typical ALS, NfH higher in ALS of more rapid progression.	NfH fivefold higher in ALS than in controls and tenfold higher than in AD	NA
Lu 2015[24]	Longitudinal, observational (two cohorts)	Serum or plasma and CSF (Gaiottino et al., 2013)[25]	167 ALS 78 HC	Blood levels of NfL higher in fast progressors and stable over time.	NfL levels higher in patients with ALS than in HC in the CSF (sensitivity 97%, specificity 95%) and blood (sensitivity 89% and 90%, specificity 75% and 71%); blood NfL level was a strong, independent predictor of survival.	NA
Steinacker 2016[26]	Cross-sectional, observational	NfL CSF (ELISA IBL), pNfH CSF (ELISA Biovendor Total Tau (CSF Innogenetics) pTau (CSF Innogenetics)	242 ALS, 11 PLS 85 MND mimics 28 AD 26 parkinsonian syndromes, 63 HC	No significant differences in neurofilament levels between sporadic and genetic ALS or PLS.	CSF NfL diagnostic sensitivity 77%, specificity 85%; CSF NfH, diagnostic sensitivity 83%, specificity 77% for MND when compared with MND mimics.	NA
Weydt 2016[27]	Cross-sectional, observational	NfL, CSF (ELISA IBL), blood (ECL, Gaiottino et al., 2013)[25], NfH, CSF (ELISA Biovendor)	12 presymptomatic mutation carriers, 64 symptomatic mutation carriers, 19 HC	Sudden increase of CSF and blood levels of NfL and NfH with ALS clinical onset.	CSF and blood NfL and CSF NfH levels higher in people with symptomatic ALS than in people who carry genet mutations but are asymptomatic, in whom levels were not higher than in HC.	NA
Benatar 2018[28]	Cross-sectional and longitudinal, prospective, observational	NfL, CSF, serum (ECL, MSD)	84 presymptomatic mutation carriers, 17 ALS patients, 10 ALS phenoconverters, 34 controls	Blood NfL concentrations stable over time. NfL levels elevated in phenoconverters above the range of controls, as far back as ~12 months preceding clinical onset.	Serum and CSF NfL higher in people with ALS than in people who carry mutations but are presymptomatic and with controls.	NA
Feneberg 2018[29]	Cross-sectional, observational multicentre.	NfL, CSF (ELISA Uman Diagnostics), serum (Simoa, Disanto et al., 2017)[7] NfH, CSF (Biovendor)	54 early symptomatic, 135 late symptomatic ALS 64 OND, 27 MND mimics, 21 other MND	No variation in NfL or NfH values across clinical diagnostic categories of ALS in the early symptomatic phase.	CSF and serum NfL levels higher in people with ALS than in controls (AUC 0.92–0.99, sensitivity 78–100% and specificity 86–98%, depending on control group); baseline NfL and NfH levels were not different among people with ALS with clinical progression at follow-up.	NA

Verde 2019[30]	Cross-sectional and longitudinal, observational, prospective	NfL, serum (Simoa)	124 ALS, 50 controls, 44 ALS mimics, 20 FTD, 20 AD, 19 PD, 6 CJD	Serum NfL correlated with disease progression rate. Serum NfL did not differ among patients in different ALS pathological stages. NfL levels were stable over time.	Serum NfL levels were higher in ALS than in all other categories except for CJD (AUC 0.887, 85.5% sensitivity and 81.8% specificity). Higher levels in ALS than ALS mimics (AUC 0.873, 85.5% sensitivity and 77.3% specificity). Higher NfL levels were associated with shorter survival.	No difference in NfL levels between patients taking and those not taking riluzole at the time of blood sampling.
Benatar 2020[31]	Longitudinal, observational, prospective, multicenter.	NfL, CSF, serum (Simoa) NfH, CSF, serum (3 assays: Simoa, in-house assay, Iron HorseDiagnostics; Euroimmun)	229 ALS, 20 PLS, 11 PMA	NA	Baseline serum NfL levels, but not pNfH, were associated with future ALSFRS-R slope and survival.	The inclusion of baseline serum NfL as a covariate into mixed effects models with ALSFRS-R as outcome reduced the estimated sample size for an ALS trial. The use of serum NfL as a pharmacodynamic marker instead of the ALSFRS-R slope as the outcome reduced the sample size.
Miller 2022[32]	Phase 3, RCT. Secondary end points: change from baseline to Week 28 in plasma NfL	NfL, plasma (Simoa)	72 ALS with *SOD1* mutations receiving tofersen, 36 receiving placebo (fast progressors in both groups).	NA	NA	Mean concentration of plasma NfL reduced by 60% in faster-progression subgroup, which received tofersen, and increased by 20% in faster-progression group, which received placebo (between-group difference in geometric mean ratio, 0.33, 95% CI 0.25–0.45)
Thompson 2022[33]	Longitudinal, observational prospective, multicentre. Age-adjusted models.	NfL, CSF, plasma (ECL, MSD)	258 ALS, 80 OND 101 HC	Small increase in longitudinal plasma NfL levels within the first 12 months after symptom onset, then stable levels. Longitudinal CSF NfL levels remained stable.	Baseline plasma and CSF NfL were higher in people with ALS than in other groups. Baseline plasma NfL was associated with survival and disease progression rate.	The use of plasma NfL, instead of the ALSFRS-R as an outcome measure significantly reduced the sample size needed.

AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; ALSFRS-R, Revised ALS Functional Rating Scale; AUC, Area under the curve; CJD, Creutzfeldt–Jakob disease; CSF, Cerebrospinal fluid; ECL, Electrochemiluminescence; FTD, Frontotemporal dementia; HC, Healthy controls; MND, motor neuron disease; NA, not applicable; NfH, Neurofilament heavy chain; NfL, neurofilament light chain; OND, other neurological conditions; PD, Parkinson disease; PLA, primary lateral sclerosis; PMA, progressive muscular atrophy; pNfH, phosphorylated NfH; RCT, randomized controlled trial.

Supplementary Table 4 | Key studies supporting the clinical use of blood neurofilaments in PD and atypical parkinsonian syndromes.

Study	Study design and data analysis	Sample type, assay used	Participants	Association with disease severity	Diagnostic and/or prognostic relevance
Hansson 2017[34]	Cross-sectional, observational, multicentre	NfL, blood (Simoa)	244 PD, 88 MSA, 70 PSP, 23 CBS, 79 HC	NA	Higher blood NfL in people with MSA, PSP and CBS than in people with PD as well as healthy controls. In all cohorts, high blood NfL accuracy in the distinction between PD and APS (AUC 0.81–0.91, 70–82%% sensitivity and 80–91% specificity)
Donker Kaat 2018[35]	Cross-sectional, observational, mono-centric	NfL, serum (Simoa)	131 PSP, 95 HC	High NfL levels associated with more severe functional, motor and cognitive disability.	Serum NfL higher in people with PSP than in HC. Association between high NfL levels and shorter survival in PSP.
Marques 2019[36]	Longitudinal, observational, mono-centric	NfL, serum (Simoa) NfL CSF (IBL)	55 PD 22 MSA, 7 PSP 53 HC	NfL already elevated at a clinical stage when final diagnosis was unclear. Diagnosis was made after 3 years of follow up.	Serum NFL levels were elevated and differentiated the atypical parkinsonism disorders group from PD (sensitivity 86%, specificity 85%).
Mollenhauer 2020[37]	Longitudinal, observational, multicentre.	NfL, CSF, serum (CSF: ELISA Uman-Diagnostics, serum: Simoa)	871 PD, 63 prodromal cases, 309 asymptomatic mutation carriers, 369 OND, 268 HC	Longitudinal increase of serum NfL in people with PD vs HC. Correlations between longitudinal change in serum NfL and MDS-UPDRS total score and some cognitive measures.	Highest baseline median serum NfL in people with OND, followed by people with genetic PD, prodromal PD, PD, mutations but no symptoms and HC. Serum NfL higher in people with PD than in HC at each of the six time points during the first 5 years after diagnosis.
Ye 2021[38]	Cross-sectional, observational, multicentre	NfL, serum (Simoa)	376 de novo PD	Associations between higher baseline levels of serum NfL and more severe parkinsonism as measured by UPDRS-III and total UPDRS scores.	Associations between baseline NfL and faster increase in UPDRS-III scores, greater exacerbation of postural instability and gait disorder scores, and greater reduction of putamen DAT binding ratio over time.
Vijiaratnam 2022[39]	Cross-sectional, observational, multicentre (longitudinal clinical follow-up data)	NfL, serum (Simoa)	291 PD (within 3.5 years of diagnosis)	Association between serum NfL and baseline cognitive scales.	Association between higher baseline levels of serum NfL and more rapid disease progression, shorter time to dementia, postural instability and death. The combination of clinical, NfL and genetic data produced a stronger prediction of unfavourable outcomes than age and gender.
Chelban 2022[40]	Cross-sectional and longitudinal, observational, multicentre	NfL, CSF, plasma (Simoa)	212 MSA, 40 HC	NfL levels increase as the motor symptoms progress, followed by deceleration in advanced stages. Correlation between plasma NfL at baseline and clinical disease severity.	Plasma NfL higher in people with MSA than in HC. Higher plasma NfL values at baseline associated with more rapid progression and shorter overall survival. Baseline plasma NfL predicted clinical progression, survival, and degree of brain atrophy. After incorporating plasma NfL as an outcome measure into clinical trials, sample size required decreased.

CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; HC, healthy controls; MSA, multiple system atrophy; NA, not applicable; OND, other neurodegenerative diseases; PD, Parkinson disease; PSP, progressive supranuclear palsy; UPDRS, Unified Parkinson's Disease Rating Scale.

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