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Diagnostic Value of Cerebrospinal Fluid Neurofilament Light Protein in Neurology
A Systematic Review and Meta-analysis

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IMPORTANCE Neurofilament light protein (NfL) is elevated in cerebrospinal fluid (CSF) of a number of neurological conditions compared with healthy controls (HC) and is a candidate biomarker for neuroaxonal damage. The influence of age and sex is largely unknown, and levels across neurological disorders have not been compared systematically to date.

OBJECTIVES To assess the associations of age, sex, and diagnosis with NfL in CSF (cNfL) and to evaluate its potential in discriminating clinically similar conditions.

DATA SOURCES PubMed was searched for studies published between January 1, 2006, and January 1, 2016, reporting cNfL levels (using the search terms *neurofilament light* and *cerebrospinal fluid*) in neurological or psychiatric conditions and/or in HC.

STUDY SELECTION Studies reporting NfL levels measured in lumbar CSF using a commercially available immunoassay, as well as age and sex.

DATA EXTRACTION AND SYNTHESIS Individual-level data were requested from study authors. Generalized linear mixed-effects models were used to estimate the fixed effects of age, sex, and diagnosis on log-transformed NfL levels, with cohort of origin modeled as a random intercept.

MAIN OUTCOME AND MEASURE The cNfL levels adjusted for age and sex across diagnoses.

RESULTS Data were collected for 10 059 individuals (mean [SD] age, 59.7 [18.8] years; 54.1% female). Thirty-five diagnoses were identified, including inflammatory diseases of the central nervous system (n = 2795), dementias and predementia stages (n = 4284), parkinsonian disorders (n = 984), and HC (n = 1332). The cNfL was elevated compared with HC in a majority of neurological conditions studied. Highest levels were observed in cognitively impaired HIV-positive individuals (iHIV), amyotrophic lateral sclerosis, frontotemporal dementia (FTD), and Huntington disease. In 33.3% of diagnoses, including HC, multiple sclerosis, Alzheimer disease (AD), and Parkinson disease (PD), cNfL was higher in men than women. The cNfL increased with age in HC and a majority of neurological conditions, although the association was strongest in HC. The cNfL overlapped in most clinically similar diagnoses except for FTD and iHIV, which segregated from other dementias, and PD, which segregated from atypical parkinsonian syndromes.

CONCLUSIONS AND RELEVANCE These data support the use of cNfL as a biomarker of neuroaxonal damage and indicate that age-specific and sex-specific (and in some cases disease-specific) reference values may be needed. The cNfL has potential to assist the differentiation of FTD from AD and PD from atypical parkinsonian syndromes.

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Supplemental content

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Identifying neuroaxonal damage and quantifying the intensity of this process is a critical step in patient care because it may support diagnosis and help estimate the prognosis of neurological conditions. In addition, it is essential for the evaluation of drug candidates with disease-modifying potential. Neurofilament light protein (NfL) is an abundant cytoskeletal protein exclusively expressed by central and peripheral neurons. Elevated levels of NfL in cerebrospinal fluid (CSF) were first reported in neurodegenerative conditions more than 20 years ago,[1] sparking interest in the potential of this neuron-specific protein as a biomarker. Since then, elevated levels of NfL in CSF (cNfL) have been described in a number of neurological and psychiatric conditions. The magnitude of the increase in inflammatory, degenerative, infectious, ischemic, and traumatic neurological conditions, as well as in psychiatric disorders, varies between conditions and studies. To date, cNfL levels have not been compared systematically between neurological disorders, and patient numbers in individual studies are often low. A positive association between cNfL and age has been reported in healthy controls (HC)[2] but was not systematically investigated in neurological conditions and may alter the performance of this biomarker across age categories. Together, these questions limit clinical implementation of cNfL. To compare cNfL levels between diagnoses, assess the association of age and sex with these variables, and evaluate the potential of cNfL level as a diagnostic biomarker, we performed a systematic review and meta-analysis on individual data collected from studies reporting cNfL levels in diseases and controls.

Key Points

Question How do levels of neurofilament light in cerebrospinal fluid (cNfL) compare between neurological conditions and with healthy controls?

Findings Among 10 059 individuals in this systematic review and meta-analysis, cNfL was elevated in most neurological conditions compared with healthy controls, and the magnitude of the increase varies extensively. Although cNfL overlaps between most clinically similar conditions, its distribution did not overlap in frontotemporal dementia and other dementias or in Parkinson disease and atypical parkinsonian syndromes.

Meaning The cNfL is a marker of neuronal damage and may be useful to differentiate some clinically similar conditions, such as frontotemporal dementia from Alzheimer disease and Parkinson disease from atypical parkinsonian syndromes.

Methods

Search Strategy

This systematic review and meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[3] We searched PubMed for articles published in English between January 1, 2006, and January 1, 2016, reporting cNfL levels (using the search terms *neurofilament light* and *cerebrospinal fluid*) in neurological or psychiatric conditions and/or in HC. Titles and abstracts were reviewed, and relevant studies were selected. The quality of primary articles was assessed using relevant criteria from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[4] and the QUADAS-2 guidelines.[5] All studies were approved by local ethics committees.

Inclusion Criteria

Studies were included if lumbar cNfL was reported for neurological patients and/or HC and/or individuals with subjective neurological or cognitive complaints and/or a psychiatric condition and/or a systemic disease that may affect the central nervous system (CNS). A reference method for the measurement of cNfL is lacking to date. To limit between-cohort heterogeneity due to the measurement tool, we included only those studies that used the same commercially available immunoassay (NF-light ELISA [enzyme-linked immunosorbent assay]; UmanDiagnostics) on the market since 2006. This assay was selected because it was used in a majority of publications (71 of 112) since 2006 and was reported to be sensitive and robust.[6]

Data Collection

We contacted the corresponding authors to request access to individual-level cNfL, age at CSF sampling, sex, and diagnosis. An individual's data were included only if all of those variables were available. For patients with multiple sclerosis (MS) and HIV-positive individuals, treatment status was also collected.[7,8] Information on study procedures was extracted from the publication or requested from the corresponding author.

Diagnostic Categories

Diagnosis was established by the original study authors according to published criteria when applicable (**Table 1**). Information about the clinical subtype of neurodegenerative conditions was not retained, and all clinical subtypes of a condition were pooled in a single diagnostic group. Stroke, cardiac arrest, HIV infection, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Guillain-Barré syndrome (GBS), Cushing disease in remission, and optic neuritis (ON) were diagnosed according to clinical guidelines. Presymptomatic genetic frontotemporal dementia (pgFTD), Huntington disease (HD), and premanifest HD (pHD) were diagnosed by genetic testing. The HIV-infected individuals with cognitive impairment (iHIV) included individuals with mild neurocognitive impairment and individuals with HIV-associated dementia.

Individuals with subjective neurological complaint (SNC) or subjective cognitive decline (SCD) had complaints but no objectifiable neurological condition after extensive workup. Inflammatory neurological diseases (IND) were inflammatory diseases of the CNS, excluding MS, clinically isolated syndrome (CIS), and ON. Noninflammatory neurological diseases (NID) were any CNS disease that was not of inflammatory nature. Mixed dementia (MD) was dementia of assumed mixed pathology, and dementia not specified (DNS) was dementia of uninvestigated origin. Healthy controls were individuals who did not have neurological complaints or signs of a neurological condition.

Diagnostic Groups

We clustered a subset of frequent neurological conditions into 3 groups of clinically similar disorders. These included the following: (1) untreated relapsing-remitting MS (uRRMS), individuals with relapsing-remitting MS treated with disease-modifying therapy (tRRMS), CIS, ON, primary progressive MS (PPMS), secondary progressive MS (SPMS), and IND; (2) Alzheimer disease (AD), FTD, combined FTD and amyotrophic lateral sclerosis (FTD/ALS), vascular dementia (VaD), dementia with Lewy bodies (DLB), idiopathic normal-pressure hydrocephalus (iNPH), mild cognitive impairment of suspected AD pathology (MCI), SCD, and iHIV; and (3) Parkinson disease (PD), PD dementia (PDD), DLB, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal syndrome of suspected tau underlying pathology (CBS).

cNfL Measurement

The cNfL was measured at 17 different centers using the commercially available kit (NF-light ELISA assay). The cNfL values were reported in picograms per milliliter or nanograms per liter. A systematic error in the reported concentration of cNfL was identified at 8 centers due to a misinterpretation of the assay's protocol. The protocol indicated to perform a 1:1 dilution of CSF before performing the assay. However, because this dilution is included a priori in the value assignment of the standard curve, this initial dilution should not be corrected for at calculation of the concentration. Raw NfL values obtained from the 8 implicated centers were corrected for the systematic error (divided by 2).

Statistical Analysis

We performed an individual-level meta-analysis based on cNfL measurements provided by the corresponding authors. Linear mixed-effects models were used to estimate the fixed effects of age, sex, and diagnosis on log-transformed NfL levels, with cohort of origin modeled as a random intercept, using the R packages "lme4" and "lmerTest" (R Project for Statistical Computing). Age was centered according to the mean. First, we tested all 2-way and 3-way interaction terms between all fixed effects, which were retained in the model when statistically significant. No 2-way interaction of age and sex or 3-way interaction of age, sex, and diagnosis on cNfL was observed, and the best-fitting model included all fixed effects and interaction terms for diagnosis by age and diagnosis by sex. Next, we used the R package "emmeans" to obtain marginalized change folds and 95% CI cNfL and cNfL-age slope estimates for all diagnoses and to perform post hoc pairwise comparisons between diagnoses in the mean cNfL levels and in the strength of the associations between cNfL age, adjusting *P* values for multiple testing with the Tukey procedure. Finally, we calculated point estimates of fold-change increases for each diagnostic group compared with controls for specific ages. The consequences of study variability on the results was assessed using the intraclass correlation coefficient, which reflects the proportion of variance that can be attributed to between-study variation, for the total sample and per diagnostic group (analyses for the latter were performed on models the included the fixed effects of age and sex). Values higher than 0.60 were considered to be indicative of substantial heterogeneity. The results were considered statistically significant when they had an adjusted 2-sided *P* value below .05. All analyses were performed in R version 3.4.2.

Table 1. Diagnostic Criteria Used by the Original Study Authors

Diagnosis	Abbreviation	Diagnostic Criteria
Multiple sclerosis and clinically isolated syndrome	MS and CIS	McDonald criteria,[9] 2005 revisions,[10] and 2010 revisions[11]
Alzheimer disease and mild cognitive impairment	AD and MCI	Criteria by McKhann et al[12] and IWG-2 criteria[13]
Parkinson disease	PD	United Kingdom Parkinson Disease Society Brain Bank criteria[14] and National Institute of Neurological Disorders and Stroke criteria[15]
Parkinson disease dementia	PDD	Movement Disorder Task Force[16]
Progressive supranuclear palsy	PSP	Criteria by Litvan et al[17]
Multiple system atrophy	MSA	Criteria by Gilman et al[18]
Corticobasal syndrome	CBS	Criteria by Lee et al,[19] criteria by Litvan et al,[17] and criteria by Mathew et al[20]
Dementia with Lewy bodies	DLB	Criteria by McKeith et al[21]
Frontotemporal dementia (including all clinical subtypes)	FTD	Criteria by Neary et al[22] and The Lund and Manchester Groups[23]
Amyotrophic lateral sclerosis	ALS	Revised El Escorial criteria[24]
Combined frontotemporal dementia and amyotrophic lateral sclerosis	FTD/ALS	
Vascular dementia	VaD	Criteria by Erkinjuntti et al[25] and National Institute of Neurological Disorders and Stroke
Idiopathic normal-pressure hydrocephalus	iNPH	Criteria by Relkin et al[26]
Bipolar disorder	BD	*Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)
HIV positive with cognitive impairment (including entire spectrum of cognitive impairment)	iHIV	Global Deficit Score[27]

Abbreviation: IWG-2, International Working Group 2.

Results

Data Set Characteristics, Population, and Demographics

The literature search resulted in 153 records. On the basis of title and abstract, 112 publications were selected for full-text review, and 44 data sets met our selection criteria and were included in the meta-analysis. In addition, 3 data sets unpublished at the time of data collection were provided by study authors, resulting in a total of 47 data sets (**Table 2** and eFigure 1 in the Supplement). Data were obtained for 10 059 individuals (mean [SD] age, 59.7 [18.8] years; 54.1% female), and 35 diagnoses were identified, including control groups (HC [n = 1332], SNC [n = 45], and SCD [n = 24] [eTable 1 in the Supplement]), inflammatory diseases of the CNS (CIS, ON, RRMS, SPMS, PPMS, and IND [n = 2795]) (eTable 1 in the

Table 2. Data Sets Included in the Meta-analysis

Source	Contributed Diagnostic Categories (No. of Individuals)	Diagnostic Criteria	Healthy Controls Contributed, No.
Anckarsäter et al,[28] 2014	None	NA	34
Axelsson et al,[29] 2014	SPMS (n = 30), PPMS (n = 5)	McDonald criteria 2010 revisions[11]	14
Bäckström et al,[30] 2015	PD (n = 99), MSA (n = 11), PSP (n = 12)	PD: United Kingdom Parkinson Disease Society Brain Bank criteria[14]	30
		MSA: Criteria by Gilman et al[18]	
		PSP: Criteria by Litvan et al[17]	
Bjerke et al,[31] 2011	AD (n = 30), VaD (n = 26)	AD: Criteria by McKhann et al[12]	30
		VaD: Criteria by Erkinjuntti et al[25]	
Bjerke et al,[32] 2014 and Jonsson et al,[33] 2012	MCI (n = 31)	Criteria by McKhann et al[12]	15
Bruno et al,[34] 2012	None	NA	19
Burman et al,[35] 2014	RRMS (n = 43), SPMS (n = 20), National Institute of Neurological Disorders and Stroke (n = 7), SNC (n = 6)	McDonald criteria 2010 revisions[11]	2
Fialová et al,[36] 2013	CIS (n = 32), RRMS (n = 18)	McDonald criteria 2005 revisions[10]	24
Fialová et al,[37] 2017	AD (n = 25), DNS (n = 13), IND (n = 17)	AD: Criteria by McKhann et al[12]	25
Gunnarsson et al,[38] 2011	RRMS (n = 92)	McDonald criteria 2010 revisions[11]	0
Hall et al,[39] 2012 and Hall et al,[40] 2015	AD (n = 48), PD (n = 196), PDD (n = 56), PSP (n = 53), MSA (n = 67), CBS (n = 15), DLB (n = 69)	AD: Criteria by McKhann et al[12]	150
		PD: National Institute of Neurological Disorders and Stroke criteria[15]	
		PDD: Movement Disorder Task Force[16]	
		MSA: Criteria by Gilman et al[18]	
		PSP and CBS: Criteria by Litvan et al[17]	
		DLB: Criteria by McKeith et al[21]	
		CBS: Criteria by Mathew et al[20]	
Herbert et al,[41] 2015	PD (n = 64), MSA (n = 50)	PD: United Kingdom Parkinson Disease Society Brain Bank criteria[14]	70
		MSA: Criteria by Gilman et al[18]	
Hjalmarsson et al,[42] 2014	Stroke (n = 20)	Clinical	20
Jakobsson et al,[43] 2014 and Rolstad et al,[44] 2015	BD (n = 133)	*Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)	38
Jeppsson et al,[45] 2013	iNPH (n = 27)	Criteria by Relkin et al[26]	20
Jessen Krut et al,[46] 2014	iHIV (n = 13)	Global Deficit Score[27]	152
Khademi et al,[2] 2013 Aeinehband et al,[47] 2015, and unpublished data	CIS (n = 203), RRMS (n = 682), IND (n = 387), National Institute of Neurological Disorders and Stroke (n = 370)	McDonald criteria[9]	30
Khalil et al,[48] 2013	CIS (n = 47), NID (n = 15)	McDonald criteria 2010 revisions[11]	0
Kuhle et al,[49] 2013	CIS (n = 62), RRMS (n = 38), SPMS (n = 25), PPMS (n = 23)	McDonald criteria 2005 revisions[10]	72
Kuhle et al,[50] 2013	RRMS (n = 30)	McDonald criteria 2005 revisions[10]	0
Kuhle et al,[51] 2015	RRMS (n = 36)	McDonald criteria 2005 revisions[10]	0
Magdalinou et al,[52] 2015 and unpublished data	AD (n = 26), CBS (n = 16), FTD (n = 16), MSA (n = 30), PD (n = 10), PSP (n = 29)	AD: Criteria by McKhann et al[12]	28
		CBS: Criteria by Mathew et al[20]	
		FTD: The Lund and Manchester Groups[23]	
		MSA: Criteria by Gilman et al[18]	
		PD: United Kingdom Parkinson Disease Society Brain Bank criteria[14]	
		PSP: Criteria by Litvan et al[17]	
Martínez et al,[53] 2015 and unpublished data	PPMS (n = 17), SPMS (n = 6), RRMS (n = 192), CIS (n = 109)	McDonald criteria[9]	0
Martínez et al unpublished data	CIS (n = 51), RRMS (n = 46)	McDonald criteria[9]	0
Martínez et al unpublished data	NID (n = 6), IND (n = 2), stroke (n = 4), GBS (n = 1), ON (n = 1)	Clinical	0
Meeter et al,[54] 2016	pgFTD (n = 42), FTD (n = 90)	Not specified	49

(continued)

Table 2. Data Sets Included in the Meta-analysis (continued)

Source	Contributed Diagnostic Categories (No. of Individuals)	Diagnostic Criteria	Healthy Controls Contributed, No.
Menke et al,[55] 2015 and Lu et al,[56] 2015	ALS (n = 38)	Revised El Escorial criteria[24]	20
Modvig et al,[57] 2013 and Modvig et al,[58] 2016	ON (n = 56)	Clinical	27
Modvig et al,[59] 2015	ON (n = 85)	Clinical	0
Paterson et al,[60] 2015	AD (n = 94)	IWG-2 criteria[13]	30
Pérez-Santiago et al,[61] 2016	iHIV (n = 14), HIV (n = 14)	Global Deficit Score[27]	0
Pijnenburg et al,[62] 2015	FTD/ALS (n = 26), FTD (n = 4), AD (n = 25), SCD (n = 24)	ALS: Revised El Escorial criteria[24]	0
		AD: Criteria by McKhann et al[12]	
		Neuropathological confirmation (11 of 25 for AD, 15 of 23 for FTD)	
		Genetic confirmation (12 of 23 for FTD)	
Pyykkö et al,[63] 2014	iNPH (n = 29), MD (n = 3), AD (n = 8)	AD: Criteria by McKhann et al[12]	0
		iNPH: Clinical	
Ragnarsson et al,[64] 2013	Cushing disease (n = 12)	Clinical	6
Romme Christensen et al,[65] 2014	PPMS (n = 12), SPMS (n = 12)	McDonald criteria 2005 revisions[10]	0
Rosén et al,[66] 2014	Cardiac arrest (n = 21)	Clinical	20
Sandberg et al,[67] 2016	RRMS (n = 97), SPMS (n = 44), PPMS (n = 12)	McDonald criteria 2010 revisions[11]	0
Scherling et al,[68] 2014	FTD (n = 83), PSP (n = 23), CBS (n = 16), PD (n = 6), AD (n = 45)	FTD: Criteria by Neary et al[22]	54
		PSP: Criteria by Litvan et al[17]	
		AD: Criteria by McKhann et al[12]	
		CBS: Criteria by Lee et al[19]	
Skillbäck et al,[69] 2014	AD (n = 1417), PDD (n = 45), FTD (n = 146), LBD (n = 114), MD (n = 517), VaD (n = 465), DNS (n = 545)	AD: IWG-2 criteria[13]	107
		DNS: *International Statistical Classification of Diseases, 10th Revision*	
		PDD: Movement Disorder Task Force[16]	
		FTD: The Lund and Manchester Groups[23]	
		DLB: Criteria by McKeith et al[21]	
		VaD: National Institute of Neurological Disorders and Stroke	
Stilund et al,[70] 2015	RRMS (n = 44), PPMS (n = 15), CIS (n = 27), SNC (n = 39)	McDonald criteria 2010 revisions[11]	0
Tortelli et al,[71] 2015 and Tortelli et al,[72] 2012	CIDP (n = 25), ALS (n = 37), MCI (n = 3), AD (n = 15), MSA (n = 1), CBS (n = 2), NID (n = 5)	ALS: Revised El Escorial criteria[24]	0
		CIDP: Clinical	
		AD and MCI: Criteria by McKhann et al[12]	
		CBS: Criteria by Lee et al[19]	
		MSA: Criteria by Gilman et al[18]	
Tortorella et al,[73] 2015	CIS (n = 21)	McDonald criteria 2005 revisions[10]	0
Trentini et al,[74] 2014	PPMS (n = 21), SPMS (n = 10), National Institute of Neurological Disorders and Stroke (n = 15)	McDonald criteria[9]	0
Vågberg et al,[75] 2015	None	NA	53
Villar et al,[76] 2015	RRMS (n = 98), CIS (n = 29)	McDonald criteria 2010 revisions[11]	37
Wild et al,[77] 2015	HD (n = 30), pHD (n = 13)	Genetic testing	14
Zetterberg et al,[78] 2016	MCI (n = 193), AD (n = 95)	Criteria by McKhann et al[12]	111

Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; BD, bipolar disorder; CBS, corticobasal syndrome; CIDP, chronic inflammatory demyelinating polyradiculopathy; CIS, clinically isolated syndrome; DLB, dementia with Lewy bodies; DNS, dementia not specified; FTD, frontotemporal dementia; FTD/ALS, combined frontotemporal dementia and amyotrophic lateral sclerosis; GBS, Guillain-Barré syndrome; HD, Huntington disease; iHIV, HIV positive with cognitive impairment; IND, inflammatory neurological disorders other than multiple sclerosis; iNPH, idiopathic normal-pressure hydrocephalus; IWG-2, International Working Group 2; MCI, mild cognitive impairment; MD, mixed dementia; MSA, multiple system atrophy; NA, not applicable; NID, noninflammatory neurological disorders; ON, optic neuritis; PD, Parkinson disease; PDD, Parkinson disease dementia; pgFTD, presymptomatic genetic frontotemporal dementia; pHD, premanifest Huntington disease; PPMS, primary progressive multiple sclerosis; PSP, progressive supranuclear palsy; SCD, subjective cognitive decline; SNC, subjective neurological complaint; SPMS, secondary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; VaD, vascular dementia.

Supplement), dementias and predementia stages (MCI, AD, pgFTD, FTD, VaD, DLB, iNPH, DNS, MD, pHD, HD, iHIV, and FTD/ALS [n = 4339]) (eTable 1 in the Supplement), and parkinsonian syndromes (PD, PDD, MSA, PSP, CBS, and DLB [n = 984]) (eTable 1 in the Supplement). Three diagnostic categories were excluded from the statistical models because they had fewer than 5 observations per sex (Cushing disease, cardiac arrest, and HIV), resulting in 32 diagnostic categories and 10 012 individuals included in the analysis.

cNfL Distribution Across Diagnoses

We first examined the distribution of cNfL across diagnostic categories (**Figure 1**). The cNfL was increased compared with HC in most neurological conditions (Figure 1A). The fold changes compared with HC varied extensively between individual conditions, with the largest effect sizes observed in iHIV (21.36; 95% CI, 9.86-46.30), FTD/ALS (10.48; 95% CI, 4.85-22.67), ALS (7.58; 95% CI, 4.49-12.81), and HD (5.88; 95% CI, 2.43-14.27) (Figure 1B; eTable 2 in the Supplement).

Association of cNfL With Age and Sex

In HC, we observed a yearly increase of 3.30% (95% CI, 2.98%-3.62%) in cNfL levels (eTable 2 in the Supplement). A positive association between cNfL and age was also observed in individuals with subjective complaints, BD, and in most neurodegenerative conditions (eTable 2 in the Supplement). In MS, iHIV, and rapidly progressive neurodegenerative conditions (FTD, ALS, FTD/ALS, MSA, PSP, CBS, and HD), no such association was observed (eTable 2 in the Supplement). In HC, cNfL was higher in men (26.0%, 95% CI, 16.0%-37.0%) (eTable 3 in the Supplement). This was also the case in a minority of neurological conditions, including MS, AD, VaD, and PD (eTable 3 in the Supplement).

cNfL Levels Within 3 Groups of Clinically Similar Disorders

We next compared cNfL between neurological conditions within 3 groups of clinically similar disorders. In inflammatory conditions of the CNS, the mean cNfL levels were similar in ON, CIS, and MS subtypes (eTable 4A in the Supplement). The association between cNfL and age was positive in ON, CIS, and IND but was negative in uRRMS (**Figure 2**A; eFigure 2 and eTable 2 in the Supplement). The ratio of cNfL between ON and CIS, ON and IND, and CIS and IND remained stable across the age range of the study, while the ratio between uRRMS and CIS decreased with increasing age (eTable 5A in the Supplement). No association between cNfL and age was observed in tRRMS and PPMS (Figure 2A and eTable 4 in the Supplement). The ratio of cNfL between uRRMS and tRRMS and between uRRMS and PPMS remained stable across the age range of the study (eTable 5B in the Supplement). No association between cNfL and age was observed in SPMS (Figure 2A; and eTable 2 in the Supplement). Although cNfL levels tended to be higher in young uRRMS compared with age-corresponding SPMS, this did not reach statistical significance (eTable 5C in the Supplement). In dementias and related disorders, the mean cNfL levels were statistically significantly higher in FTD compared with other causes of dementia, such as AD (2.08; 95% CI, 1.72-2.56 [eTable 4B in the Supplement]), VaD (1.56; 95% CI, 1.25-1.96 [eTable 4B in the Supplement]), and DLB (2.50; 95% CI, 1.89-3.33 [eTable 4B in the Supplement]). An association of cNfL with age was positive in AD, VaD, and DLB but was absent in FTD (Figure 2B; eFigure 2B and eTable 4B in the Supplement). The ratio of cNfL between AD and FTD increased with age; in individuals 90 years and older, the distribution of cNfL in both conditions overlapped (eTable 5D in the Supplement). An association between cNfL and age was absent in FTD and FTD/ALS, while it was present in pgFTD (eFigure 2 and eTable 2 in the Supplement). A positive association with age was observed in AD, MCI, and SCD (Figure 2B; eTable 2 in the Supplement), and the ratio of cNfL between AD and MCI remained stable across the age range (eTable 5E in the Supplement). In parkinsonian syndromes, the mean cNfL levels did not differ between PD and PDD and between PDD and DLB, while they were higher in MSA, PSP, and CBS compared with PD (eTable 4C in the Supplement). In MSA, PSP, and CBS, no association with age was observed, while a positive association was found in PD, PDD, and DLB (Figure 2C and eTable 2 in the Supplement). The ratio of cNfL between MSA and PD, PSP and PD, and CBS and PD decreased with age but remained high across the age range of the study (Figure 2C and eTable 5G in the Supplement).

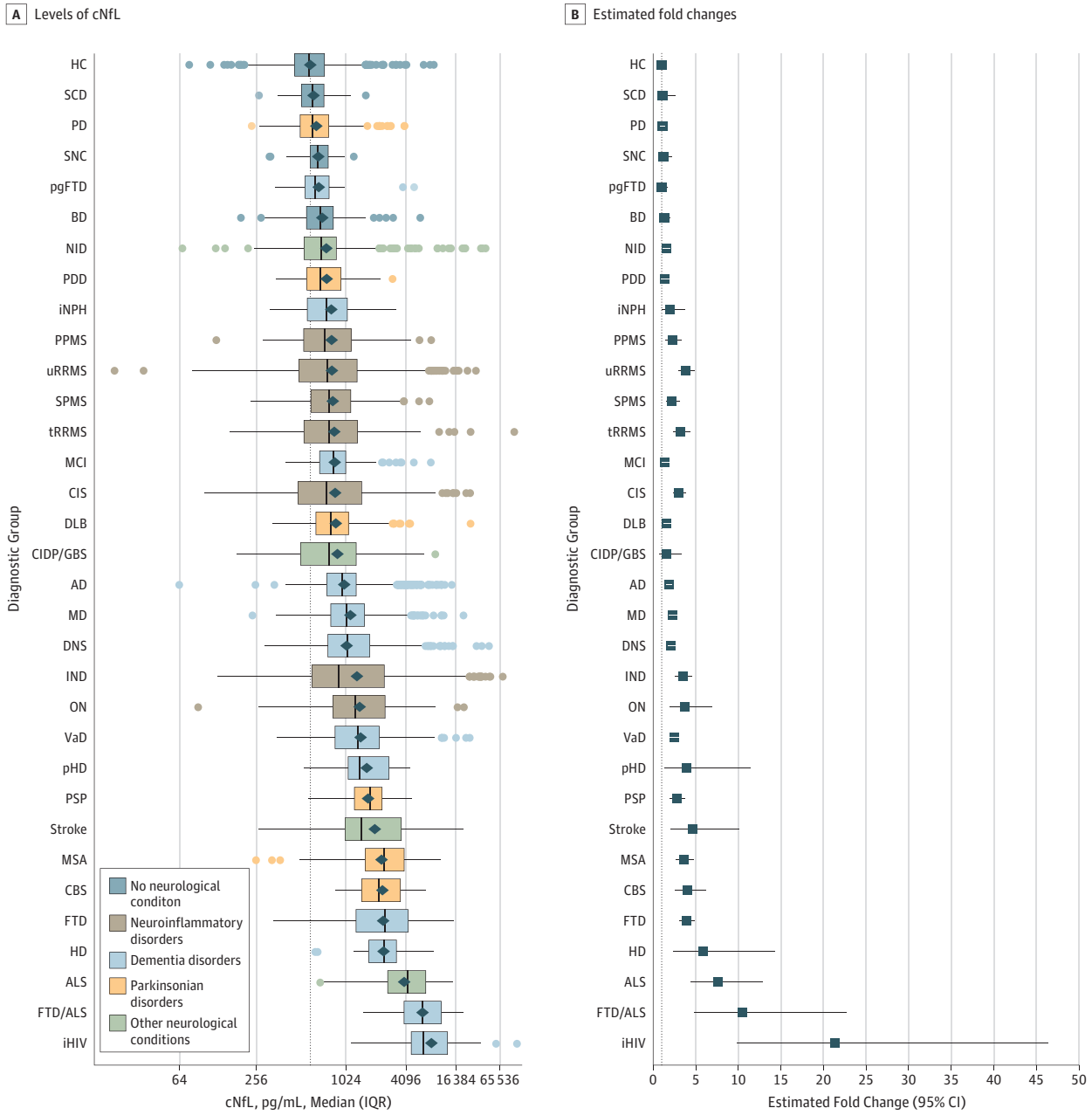
Assessment of Cohort Heterogeneity

In this meta-analysis, we pooled individual patient data originating from 42 different data sets. To estimate the proportion of the total variance of cNfL accounted for by the data set (cohort) of origin, we calculated the intraclass coefficient for cohort-related random intercepts. Across the total sample (n = 10 012), the intraclass coefficient was low at 0.15. Likewise, in a majority of diagnostic categories, the intraclass coefficient was low to moderate (<0.60). However, in 7 of the 32 diagnostic categories (MD, DNS, PDD, DLB, NID, iHIV, and stroke), the intraclass coefficients were high (>0.60), indicating that a large proportion of the variance in cNfL was due to the data set of origin (eTable 6 in the Supplement).

Discussion

In this meta-analysis that included 10 012 individuals, we found that cNfL was increased compared with HC in most neurological conditions studied. The largest effect sizes were observed in iHIV, FTD/ALS, ALS, and HD, while the effect sizes in inflammatory conditions of the CNS were low. Other neurological disorders showed much subtler increases that failed to reach statistical significance (PD and CIDP/GBS). However, the effect sizes in these conditions were positive, and larger sample sizes may allow for more robust estimates. In HC, we observed a positive association between cNfL and age. A positive association, albeit weaker, was also present in a majority of neurological conditions. An association with sex was absent in most diagnostic categories except for HC, PPMS, AD, VaD, and PD, where levels were higher in men. In clinically similar disorders, the distribution of cNfL relative to age mostly overlapped, suggesting limited use for differential diagnosis. Exceptions were FTD, which segregated from other common

Figure 1. Neurofilament Light in Cerebrospinal Fluid (cNfL) Levels Across Diagnostic Categories



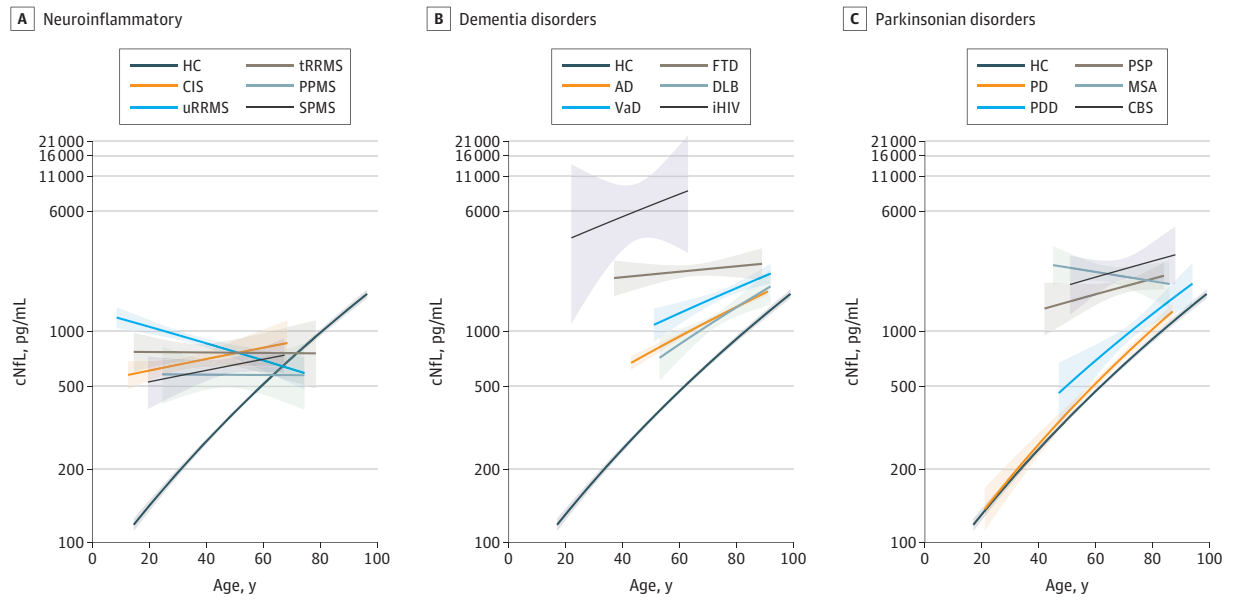
A, Levels of cNfL are shown corrected for age and sex. B, Estimated fold changes are compared with healthy controls (HC). AD indicates Alzheimer disease; ALS, amyotrophic lateral sclerosis; BD, bipolar disorder; CBS, corticobasal syndrome; CIDP/GBS, chronic inflammatory demyelinating polyradiculopathy and Guillain-Barré syndrome; CIS, clinically isolated syndrome; DLB, dementia with Lewy bodies; DNS, dementia not specified; FTD, frontotemporal dementia; FTD/ALS, combined frontotemporal dementia and amyotrophic lateral sclerosis; HD, Huntington disease; iHIV, HIV positive with cognitive impairment; IND, inflammatory neurological disorders other than multiple sclerosis; iNPH, idiopathic normal-pressure hydrocephalus; MCI, mild cognitive impairment; MD, mixed dementia; MSA, multiple system atrophy; NID, noninflammatory neurological disorders; ON, optic neuritis; PD, Parkinson disease; PDD, Parkinson disease dementia; pgFTD, presymptomatic genetic frontotemporal dementia; pHD, premanifest Huntington disease; PPMS, primary progressive multiple sclerosis; PSP, progressive supranuclear palsy; SCD, subjective cognitive decline; SNC, subjective neurological complaint; SPMS, secondary progressive multiple sclerosis; tRRMS, treated relapsing-remitting multiple sclerosis; uRRMS, untreated relapsing-remitting multiple sclerosis; and VaD, vascular dementia.

causes of dementia (including AD and VaD), and PD, which segregated from atypical parkinsonian syndromes. These data indicate that cNfL may contribute to the differentiation of these conditions, particularly in younger individuals.

cNfL and Age

In about two-thirds of the diagnoses, including HC, we observed a positive association between cNfL and age. In the control groups (HC, SNC, and SCD), as well as in pgFTD and BD,

Figure 2. Neurofilament Light in Cerebrospinal Fluid (cNfL) in Neurological Conditions According to Age



A-C, Log cNfL values are shown according to age across diagnoses. Shading around regression lines represents standard errors. AD indicates Alzheimer disease; CBS, corticobasal syndrome; CIS, clinically isolated syndrome; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; HC, healthy controls; iHIV, HIV positive with cognitive impairment; MSA, multiple system atrophy; PD, Parkinson disease; PDD, Parkinson disease dementia; PPMS, primary progressive multiple sclerosis; PSP, progressive supranuclear palsy; SPMS, secondary progressive multiple sclerosis; tRRMS, treated relapsing-remitting multiple sclerosis; uRRMS, untreated relapsing-remitting multiple sclerosis; and VaD, vascular dementia.

the association of cNfL with age was strongest. This positive association in diagnostic categories without an overt neurological condition may reflect a decrease in CSF clearance with age, the presence of a preclinical age-related neurological condition, or age-related neuronal loss.[79] The association of cNfL with age in HC implies that age-specific reference values may be needed and that the diagnostic potential of cNfL may decrease with age. In neurological conditions with substantially elevated levels of cNfL, such as FTD, ALS, FTD/ALS, HD, and iHIV, as well as in atypical parkinsonian syndromes, no association with age was observed, suggesting that neuropathological processes may cause plateau levels or mask age associations. In MS, an association with age was absent or negative, which may reflect the observation that younger patients with MS have more active diseases.[2]

cNfL and Sex

In a minority of diagnoses, including HC, cNfL was higher in men than women. The clinical relevance of these findings is uncertain, but the results suggest that sex-specific reference values may be needed.

Other Determinants of cNfL Levels

Age, sex, and the random (cohort) association explained 46% of the variance of cNfL in the best-fitting model, indicating that many determinants of cNfL remain to be identified. Disease duration and severity could influence cNfL levels. However, these data were not available in the data sets that were included in this meta-analysis, and studies designed specifically to evaluate the association of these variables and others (eg, smoking, physical activity, and body size) are ongoing.

cNfL in Inflammatory Conditions of the CNS, Including MS

The cNfL was increased in all inflammatory conditions of the CNS examined in this meta-analysis, but the effect sizes were small. The distribution of cNfL in CIS, ON, and RRMS overlapped, which may be expected because CIS and a proportion of ON are initial manifestations of RRMS. Neurodegeneration has a central role in MS, contributing to disease progression and long-term disability.[80] Poor understanding of the processes driving neurodegeneration, together with the lack of biomarkers allowing dynamic measurement of its rate, hampers the development of specific treatments.[81] The cNfL has been reported to correlate with brain atrophy,[50,82] which is considered a marker of neurodegeneration.[83,84] We found that levels of cNfL did not differ statistically significantly between RRMS, PPMS, and SPMS, indicating that on a population level cNfL may not differentiate acute inflammation-induced neuronal damage in the context of relapses from progressive neurodegeneration if the consequences of recent relapses or novel lesion formation are not considered. In individual patients, cNfL has been reported to reflect acute neuronal and axonal damage in MS, with levels transiently increasing during relapse.[85-87] We found that cNfL levels in uRRMS and tRRMS did not differ statistically significantly. However, patients with the most active RRMS with potentially highest cNfL levels are also those who are most likely to be treated, and cNfL has been reported to decrease after treatment initiation in individual patients.[38,50,51]

cNfL in Dementia and ALS

The higher levels of cNfL observed in FTD compared with other frequent causes of dementias, including AD, VaD and DLB, may be related to the anatomical location of neurodegeneration or the rate of neuronal death. This finding suggests that cNfL may support the differentiation of FTD from other dementias, in line with a recent study[88] not included in this meta-analysis, which reported that in combination with YKL40 and Aβ42 cNfL assists in the differentiation between FTD and AD with high accuracy. In iHIV, which included both mild cognitive impairment due to HIV and HIV-associated dementia, we observed highest levels of cNfL, setting it apart from neurodegenerative and vascular causes of dementia. This may reflect a high rate of neuroaxonal damage due to the presence of HIV and the inflammatory response to it in the CNS, or it may indicate additional peripheral nervous system damage contributing to the elevation of cNfL. In predementia stages, such as MCI and pgFTD, cNfL values were similar to levels in HC, suggesting that CNS damage must reach a certain extent before it is reflected by increased cNfL. However, the pgFTD cohort was small (n = 42); therefore, a small effect size could have been missed. The cNfL levels were highly elevated in ALS and FTD/ALS compared with HC. These results are in line with single-center studies not included in this meta-analysis that used different assays to measure NfL in CSF.[89] Together with the high levels of cNfL observed in stroke, these findings indicate that the rate of neuroaxonal damage may be an important determinant of the magnitude of NfL increase in CSF, possibly by overriding CSF clearance mechanisms.

cNfL in Degenerative Parkinsonian Syndromes

In degenerative parkinsonian syndromes, cNfL clustered into 2 groups. The first group consisted of PD, PDD, and DLB, in which cNfL levels were similar to those in HC, and the second group consisted of atypical parkinsonian syndromes MSA, PSP, and CBS, with elevated levels of cNfL compared with HC and the absence of association with age. This finding is in line with the results of another meta-analysis[90] that focused on parkinsonian disorders, examining data sets not included in the present meta-analysis, further underscoring the robustness of our findings. These data have important clinical implications because they suggest a potential for cNfL in supporting the differentiation of PD from atypical parkinsonian syndromes. Accurate and early differential diagnosis of these conditions is crucial because their prognosis and management differ substantially.

Serum NfL

A few years ago, an ultrasensitive assay was developed that allows measurement of NfL in serum (sNfL). This assay uses the same antibody pair as the immunoassay used in the studies included in this meta-analysis, and studies[91,92] have reported high correlations between serum and CSF levels. These findings indicate that sNfL may replace cNfL. In addition, it may likely be that the findings of the present meta-analysis, which collected data over 10 years, can be readily translated to sNfL.

Limitations of the Study

Our systematic review and meta-analysis has some limitations. In all studies included in the meta-analysis except one,[93] diagnosis was based on clinical criteria. This limitation is mostly a concern for dementias and parkinsonian syndromes, for which definitive diagnosis requires postmortem examination. However, the agreement between clinical and pathological diagnoses was reported to be high when diagnoses were established in specialized centers using consensus criteria.[94,95] For AD and MCI, 2 consensus criteria were applied (criteria by McKhann et al[12] and the International Working Group 2 [IWG-2] criteria[13]), for which a high concordance rate was reported.[96] For VaD, the 2 consensus diagnostic criteria used (criteria by Erkinjuntti et al[25] and the National Institute of Neurological Disorders and Stroke criteria) were also reported to have a high agreement.[97] For PD, 2 consensus criteria were applied, for which concordance evaluation is not available. For ALS, FTD, PSP, MSA, PDD, DLB, and iHIV, the same consensus criteria were applied in all studies. In MS, the McDonald criteria were revised over time, and this may have influenced classification of RRMS and CIS. A further limitation is the inability to capture dementia of multifactorial origin, which may have increased heterogeneity in the dementia diagnostic categories and blurred the difference in cNfL distributions between dementia subtypes. Further classification of neurodegenerative conditions into clinical phenotypes could not be performed because this information was absent in a majority of studies. Therefore, the specific value of cNfL in subphenotypes could have been missed in this meta-analysis. In addition, for some conditions, data and age ranges were limited, resulting in large standard errors and low statistical power, and conclusions for these conditions should be interpreted with caution. Finally, we included only those studies that used a specific immunoassay for cNfL in an attempt to reduce heterogeneity due to the analytical procedure. However, the range of conditions that were explored in the studies not included in the meta-analysis for the same reason did not differ from those included.

Conclusions

Our study was designed to compare cNfL levels across neurological conditions and controls, assess the association of age and sex with these variables, and evaluate the potential of cNfL to differentiate clinically similar conditions. Our meta-analysis found that cNfL was elevated in a majority of the neurological conditions included in this study. Although cNfL overlapped between most clinically similar conditions, its distribution did not overlap in FTD compared with other dementia subtypes or in PD compared with atypical parkinsonian syndromes, indicating clinical potential in differentiating these conditions.

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