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Serum Neurofilament Light Chain, Brain Infarcts, and the Risk of Stroke: A Prospective Population-Based Cohort Study

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Abstract

Neurofilament light chain (NfL), a neuron-specific protein, has been related to several neurodegenerative diseases. In addition, elevated levels of NfL have also been observed in patients admitted to the hospital for stroke, suggesting that NfL as a biomarker may extend well beyond neurodegenerative diseases. Therefore, using data from the Chicago Health and Aging Project (CHAP), a population-based cohort study, we prospectively investigated the association of serum NfL levels with incident stroke and brain infarcts. During a follow-up of 3,603 person-years, 133 (16.3%) individuals developed incident stroke, including ischemic and hemorrhagic. The HR (95%CI) of incident stroke was 1.28 (95%CI 1.10–1.50) per 1 standard deviation (SD) increase of log10 NfL serum levels. Compared to participants in the first tertile of NfL (i.e., lower levels), the risk of stroke was 1.68 times higher (95%CI 1.07 – 2.65) in those in the second tertile and 2.35 times higher (95%CI 1.45 – 3.81) in those in the third tertile of NfL. NfL levels were also positively associated with brain infarcts; 1-SD in log10 NfL levels was associated with 1.32 (95%CI 1.06 – 1.66) higher odds of one or more brain infarcts. These results suggest that NfL may serve as a biomarker of stroke in older adults.

Keywords

epidemiology; incidence; stroke; neurofilament light chain; brain infarcts; MRI

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Author contributions

Conception and design of the study (AD, CSD, NTA, KD, PJ, DE, KBR). Acquisition and analysis of data (AD, CSD, KBR). Drafting a significant portion of the manuscript or figures (AD, CSD, NTA, KD, PJ, DE, KBR).

Conflict of interest

All authors have nothing to declare.

Ethical approval

The study was approved by the Rush University Medical Center Institutional Review Board. All study participants provided written informed consent.

Introduction

Neurofilament light chain (NfL) is a neuron-specific protein that regulates the structure, size, and shape of axons [1,2]. In neurodegenerative diseases characterized by neuronal damage, axons undergo progressive granular disintegration accompanied by the release of NfL into the extracellular space that eventually reaches the cerebrospinal fluid, (CSF) and peripheral blood [3]. Therefore, increased NfL levels in the blood may indicate an ongoing neurological disorder.

Recent research studies have shown that NfL plasma levels are elevated in patients with Alzheimer's disease and related dementias [4], amyotrophic lateral sclerosis [5], multiple sclerosis [6], Parkinson's disease [7], and traumatic brain injury [8]. In addition, elevated levels of NfL have also been observed in patients admitted to the hospital for stroke [9–13], suggesting that the properties of NfL as a biomarker may extend well beyond neurodegenerative diseases (e.g., Alzheimer's disease, multiple sclerosis). However, the relationship between NfL and cerebrovascular disease, such as stroke, has been determined cross-sectionally (i.e., measuring NfL plasma concentrations at the time of a stroke or after a stroke) [14], thus its predictive abilities are understudied. In addition, most of these investigations are conducted in clinical settings [9–13], while a few studies have used the general population[15], but none have been focused on racially diverse populations. According to the American Heart Association, Blacks or African Americans have almost double the risk of incident stroke compared to Whites [16]. Therefore, utilizing data from a bi-racial population-based study in the United States, we investigated the association of serum NfL levels with incident stroke, including ischemic and hemorrhagic, during 15 years of follow-up. We also sought to determine the relationship between NfL and the presence of brain infarcts. Finally, we studied whether serum NfL levels change according to the location (i.e., cortical or subcortical), side (i.e., left or right), and size (i.e., small or large) of brain infarcts.

Methods

Study settings and population

This study is embedded within the Chicago Health and Aging Project (CHAP), a population-based cohort study in the US among individuals aged 65 years and older residing on the south side of Chicago. The CHAP study design has been described in detail previously [17]. In brief, 10,802 participants were interviewed at home every three years from 1993 to 2012. The home visits consisted of acquiring information about their demographics, lifestyle factors, and medical history obtaining blood samples [18]. For the current study, we focused on participants (n=5,696) who agreed to provide blood specimens. Of the 5,696 participants with blood samples (11,600 blood draws during the study period), we performed immunoassays to assess the NfL levels in 1,327 randomly selected individuals due to due to budgetary constraints. Details about the selection process are described previously [19]. Next, we identified people enrolled in Medicare and Medicaid Services to determine the prevalence and incidence of stroke. We also reviewed self-reported data to identify participants with stroke. Of 1,327 individuals with NfL assessments, 1,047 had information

on stroke, 230 of whom were diagnosed with stroke before (i.e., prevalent stroke) the study baseline (i.e., date of blood collection). After excluding prevalent strokes at baseline, our study sample comprised 817 individuals.

Measurement of serum concentration of NfL

After drawing blood, the phlebotomist kept the collecting tubes on dry ice and transported them to the Rush University Medical Center Biorepository freezer, where they were stored at −80°*c*. In 2019, unthawed samples were sent to Quanterix Corporation in Billerica, MA to assess NfL concentrations. The assay kit to measure the NfL included a bead-based HD-X molecular immunoassay platform and the Neurology 4Plex. Details about measuring NfL are given in our previous publications [19,20].

Assessment of demographics and other variables: Age was computed as the difference in years between the date of the blood draw and the birth date. Race and sex were provided in participants' self-responses to the structured questions of the 1990 US Census. Education level was computed as years of regular schooling. Smoking status was obtained from self-reports; in which participants responded whether they were current, former, or never smokers. Any history of hypertension, diabetes, or dyslipidemia was based on self-reports or prescriptions for the condition-specific medication (e.g., statins). The study research team visually inspected and recorded all participants' prescriptions during the in-home interviews.

Assessment of stroke

To determine the prevalence and incidence of stroke in CHAP, we reviewed the medical reports on stroke-related hospital admissions for the participants enrolled in Medicare and Medicaid Services (82% of the sample). The International Classification of Diseases Ninth Revision (ICD-9) coding (e.g., 430–438) was used to determine stroke diagnosis, including ischemic and hemorrhagic stroke, as described previously [21–23]. Of all stroke hospitalizations in CHAP, about 91% were ischemic and 9% hemorrhagic [23]. For participants not enrolled in Medicare and Medicaid Services, information on stroke events was acquired from self-reports when the study participants reported their co-morbidities, including stroke, by responding to standardized and validated questions from the Established Populations for Epidemiologic Studies of the Elderly [24].

For the current study, data on incident stroke were collected through a follow-up system from February 1995 to July 2012.

Assessment of brain infarcts: size, location, and side

CHAP participants were invited to participate in a magnetic resonance imaging (MRI) study. Of the 817 individuals included in the current study, 470 underwent MRI scans. The procedure and analyses of MRI data are described in our previous publications [25,26]. In short, individuals were imaged using a General Electric 1.5-T scanner (Excite platform, version 11; General Electric Healthcare, Milwaukee, WI), and the following imaging sequences were obtained: (1) fluid-attenuated inversion recovery (FLAIR); (2) SPGR; and (3) double-spin echo. Images were oriented parallel to a hypothetical line

connecting the anterior and posterior commissures. The digital MRI information of MRI scans was processed and analyzed by QUANTA 6.2, operating on a Sun Microsystems Ultra 5 workstation (Santa Clara, CA). Qualified investigators performing imaging analyses were blinded to personal identifying information.

The presence or absence of cerebral infarcts was determined based on the lesion's size and other imaging characteristics [25], including CSF density on the subtraction image and whether the infarct was in the basal ganglia, distinct separation from the circle of Willis's vessels, or perivascular spaces. We determined the brain infarct size, side, and location. Lesions 3 mm or larger were considered brain infarcts. The size was quantified as smaller if the brain infarct was less than 0.5 cm and larger if it was more than 0.5 cm. The side of the brain infarct was specified as either left or right side and the location of the infarct was determined as either cortical or subcortical. The reliability of the MRI measures has been previously published and was greater than 0.90 [27].

Statistical analysis

Serum concentrations of NfL were log10-transformed to obtain a normal distribution and further standardized to provide comparable regression estimates. NfL was investigated as a continuous variable for a 1-SD increase in log10 levels and as a categorical variable, i.e., tertiles, with the first tertile as a reference group.

We used Cox proportional-hazard regression models to estimate the hazard ratios (HRs) of the risk of incident stroke during the follow-up period for a 1-SD increase in log10 serum NfL levels. Participants contributed to person-time from the baseline (date of blood draw) until the date of the first stroke event. Individuals who did not develop stroke were censored to the date of death, loss to follow-up, or the end of the follow-up period. Models were adjusted for age, sex, race, education, smoking status, hypertension, diabetes, and dyslipidemia. These potential confounders were selected based on the literature and their contribution to the risk of stroke [28]. The proportional hazard assumption, assessed by the interaction between time and Schoenfeld residuals, was satisfied.

We used a binomial logistic regression model to estimate odds ratios (ORs) of the risk of brain infarcts for a 1-SD increase in log10 serum NfL levels. Because the number of cerebral infarcts had a skewed distribution, we designated participants without infarcts as a reference group and those with one or more infarcts as the at-risk group. The multivariable model was adjusted by age, sex, race, education, smoking status, hypertension, diabetes, and dyslipidemia. In addition, we computed the lag between blood draw and MRI assessment and adjusted the multivariable model to account for the role of the time gap between these assessments.

We also investigated whether serum concentrations of NfL were different according to the size, side, and location of brain infarcts. We computed adjusted means of serum log10 NfL levels in people with infarcts in the cortical and subcortical regions of the brain; in people with infarcts on the left and right sides of the brain; and in people with small and large infarcts. We contrasted the adjusted means of serum log10 NfL levels to identify the differences by location, side, and size of infarcts.

Further, we examined whether age, sex, and race modified the association of NfL with incident stroke and brain infarcts by conducting a series of interaction analyses.

Sensitivity Analysis

We conducted several sensitivity analyses to evaluate the strength of our primary findings. First, we adjusted our multivariable model by the creatine levels since kidney function is an important determinant of plasma NfL values. Second, although we adjusted our models for the lag between the blood draw and MRI assessment to account for the role of the time gap between these assessments, we also conducted additional analyses in which we focused only on individuals who had both assessments within 1 year (median of lag) and 3 years (75% of the study population had both assessments). Third, our primary analysis included both ischemic and hemorrhagic stroke, and in a sensitivity analysis, we focused on participants enrolled in Medicare and Medicaid Services and examined the association of NfL with incident ischemic and hemorrhagic stroke. Fourth, given that our study population included older individuals (i.e., the average age of 80 years) and NfL is related to dementia risk,[19] we conducted two subsequent sensitivity analyses. In the one analysis, we adjusted our multivariable models with global cognition at the study baseline (i.e., blood draw). In the other analysis, we controlled for neurodegenerative diseases, including incident Alzheimer's dementia, Parkinson's disease, and Multiple sclerosis, during the study period. Fifth, although our primary biomarker of interest was NfL, given the literature support of the role of NfL on stroke, we also evaluated two other biomarkers neurodegeneration, such as total tau (t-tau) and glial fibrillary acidic protein (GFAP).

Analyses were performed using the R program, version 4.1 (R Group for Statistical Computing). Our a priori cutoff for statistical significance was a *P*-value < 0.05.

Results

The baseline demographic and clinical characteristics of the study population are presented in Table 1. On average, participants were 81 years old at the baseline, 62% were women, and 59% were African Americans. Individuals with higher levels of NfL (i.e., third tertile) were older (84 vs. 78 years) and had a higher prevalence of diabetes and hypertension. The baseline characteristics of individuals who underwent MRI scanning are presented in S1 Table. Individuals with MRI data were similar in age, sex, and race to the overall study sample.

NfL and Risk of Stroke

Table 2 shows the association of serum concentrations of NfL with the incident of stroke. During 3,603 person-years of follow-up, 133 individuals developed the first stroke event. In the multivariable-adjusted model, a 1-SD increase in log10 NfL levels was associated with a 1.28 times higher risk of developing stroke (HR: 1.28; 95%CI 1.10–1.50) risk of developing stroke. In addition, compared to individuals with lower levels of NfL -in the first tertile-, those in the second and third tertiles had HRs of 1.68 (95%CI: 1.07–2.65) and 2.35 (95%CI: 1.45–3.81) for the incident stroke, respectively.

NfL and Brain Infarcts

Table 3 presents the association between serum NfL levels and brain infarcts among participants who underwent the MRI scan. We determined the presence of infarcts in the brain if the lesions were 3 mm or larger, independent of the history of stroke. Among 470 individuals with MRI data, 120 (25.5%) had brain infarcts. In the multivariable-adjusted model, a 1-SD increase in log10 NfL levels was associated with 1.32 higher odds of one or more brain infarcts (OR: 1.32; 95%CI: 1.06 – 1.66). In addition, compared to individuals in the first tertile of NfL, those in the second and third tertiles had ORs of 1.85 (95%CI: 1.07–3.22) and 2.03 (95%CI: 1.14–3.66), respectively.

Figure 1 shows the adjusted mean of serum NfL levels by the location (i.e., cortical or subcortical region), side (i.e., left or right), and size (i.e., small or large) of brain infarcts. There were no significant differences in serum NfL levels comparing individuals with brain infarcts (located) in the cortical vs. the subcortical region (adjusted *P* value = 0.96). Similarly, no differences in NfL levels were found when the brain infarcts were on the left or the right side of the brain (adjusted *P* value = 0.99). There was also no difference in the serum NfL levels according to the infarct size (small v.s. large; adjusted *P* value = 0.99).

No significant (i.e., *P*-value > 0.05) interactions between serum NfL concentrations and age, sex, or race were noted when we investigated their respective association with brain infarcts and incident stroke.

Sensitivity Analysis

The association between NfL levels and the risk of incident stroke during the follow-up did not change (HR after additional plasma creatinine levels adjustment (S2 Table). S3 Table shows the association of NfL with brain infarcts according to the lag time between blood draw and MRI assessment. Results of analyses, including participants who had a blood draw and MRI assessment within 1 year and those within 3 years, showed similar associations to the main findings, OR (95%CI) were 1.40 (1.04–1.92) and 1.59 (1.22–2.13), respectively. Focusing the analysis on participants enrolled in Medicare and Medicaid Services, we examined the association of NfL with incident ischemic (n=94, 89.5%) and hemorrhagic stroke (n=11, 10.5%), which showed similar findings to overall stroke. HR (95%CI) for ischemic and hemorrhagic stroke were 1.28 (1.06–1.55) and 1.90 (1.30–2.79), respectively (S4 Table). Additional adjustments for global cognitive function at the baseline (S5 Table Model A) or neurodegenerative diseases, including incident Alzheimer's dementia, Parkinson's disease, and Multiple sclerosis during study follow-up (S5 Table Model B), did not modify the estimated coefficients between NfL concentrations and the risk of incident stroke (HR 1.29, 95%CI 1.1 – 1.51). S6 Table shows the associations of t-tau and GFAP blood concentrations and incident stroke. Both biomarkers were not significantly associated with the risk of incident stroke, albeit the regression coefficients of t-tau with stroke were similar to NfL.

Discussion

In this prospective population-based cohort study, we found that higher serum NfL levels were associated with an increased risk of incident stroke during the follow-up period. In addition, NfL concentrations were higher in people with brain infarcts than those without infarcts, as determined by an MRI scan. Among people with brain infarcts, NfL levels could not differentiate between large vs. small brain infarcts or infarcts in the cortical vs. subcortical region or located in the left or right hemisphere.

Clinical studies have examined the relationship between plasma/serum levels of NfL and stroke, but have primarily focused on the functional prognosis after stroke [9–13]. For example, a recent meta-analysis demonstrated that stroke patients with higher levels of NfL had a 1.71 times higher risk of adverse functional outcomes during a 3-month follow-up period [29]. In addition, these studies showed that the timing of when blood is drawn to assess NfL levels has an effect on the predictive ability of NfL and suggests that assessing NfL levels within 24 hours after stroke onset makes NfL a better predictive biomarker for the functional outcome of ischemic stroke [29,30]. In our study, the focus was to examine whether baseline serum NfL is associated with the future risk of stroke. We showed that NfL concentrations assessed years before the occurrence of the stroke is associated with an increased risk of the stroke event. Therefore, in addition to being a biomarker of stroke prognosis, NfL can also inform about the risk of incident stroke. However, evidence linking NfL with incident stroke is limited. In an earlier European study, researchers found a higher risk of stroke in people with increasing concentrations of NfL [15]. Utilizing data from the Rotterdam Study, investigators showed that per 1-SD increase in log_2 NfL, the risk of stroke increased by 27% during the follow-up period [15]. Another study focusing on people with diabetes went further and examined whether measures of NfL could increase the discriminatory power of the traditional risk factors in predicting incident stroke [31]. This cohort study of middle-aged adults with diabetes showed that NfL improved C statistics from 0.71 to 0.78. Although the overall literature is limited on the topic, these studies, including the current study, suggest that NfL is associated with the risk of incident stroke [31].

In addition, serum NfL levels were also related to the presence of a brain infarct on MRI. Studies investigating the association of NfL with brain infarcts attribute increased serum NfL levels to neuroaxonal injury [29]. For example, an investigation of individuals admitted to the hospital for ischemic stroke demonstrated that patients with stroke had higher NfL levels from admission until six months post-stroke than those without stroke [32]. In addition to direct ischemic injury, other potential mechanisms described in the literature are related to immune and inflammatory responses to brain infarcts [29,33,34]. The onset of stroke can provoke an inflammatory cascade response accompanied by increased NfL levels. However, additional epidemiological and experimental studies are necessary to understand the pathophysiology of NfL in stroke, especially how NfL levels measured years before the onset of stroke predict the risk of the incident ischemic and hemorrhagic stroke.

In our study, we found that NfL was associated with incident stroke, but t-tau and GFAP were not (sensitivity analysis). NfL and t-tau have similarities because both are related to the

structure of neurons, while GFAP is a protein related to the structure of astrocytes. Although the association between t-tau and stroke did not reach statistical significance, the regression coefficients were similar to NfL-stroke, suggesting similar underlying mechanisms related to vascular disease in the brain [15].

Our study has several limitations. First, we do not have measures of NfL CSF to validate the correlation between serum NfL levels and CSF in our study. Second, the assessment of NfL was conducted on participants who agreed to provide blood samples, limiting the possibility of generalizing our results to the general population. Third, while the majority of stroke events were determined by reviewing Medicare and Medicaid Services data, for participants not enrolled in the services, information on stroke occurrence was acquired from self-reports, which is prone to recall bias. In addition, the absolute number of cases of hemorrhagic stroke was small, limiting the statistical inferences for the association between NfL and incident hemorrhagic stroke. However, our associations were supported by the findings on NfL and brain infarcts determined by the MRI. Fourth, our investigation was based on observation data prone to residual confounding, and we can not assume causality based on the reported associations. Fifth, the analysis of the mean differences in serum NfL levels by the location, side, and size of brain infarcts were underpowered and should be further investigated in future studies. Sixth, the relatively smaller sample size limits a thorough analysis of NfL levels and race. The strengths of our study include the study design, a biracial prospective population-based sample with a long follow-up time for incident stroke, and the availability of data on NfL and a range of confounders.

In conclusion, individuals with higher serum NfL levels had an increased risk of stroke and a greater number of brain infarcts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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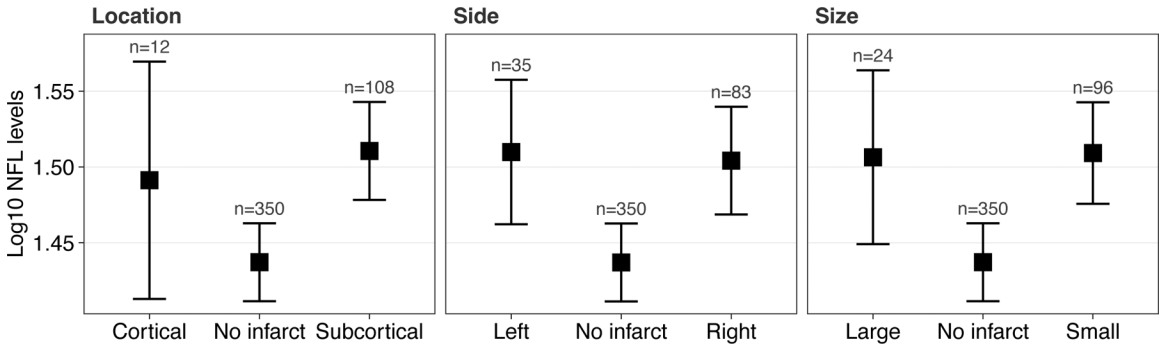

Figure 1: NFL levels by location, size, and side of the brain infarcts.

The figure shows the adjusted mean ± standard errors of plasma NFL levels by location (i.e., cortical and subcortical), side (i.e., left and right), and size (i.e., small and large) of brain infarcts. Means are adjusted by age, sex, race, education, smoking, hypertension, diabetes, dyslipidemia, and time from blood draw to MRI assessments.

There were no significant differences in plasma log10 NFL levels when we compared brain infarcts by location (cortical v.s. subcortical; adjusted *P* value = 0.96), side (left v.s. right; adjusted *P* value = 0.99), or size (small v.s. large; adjusted *P* value = 0.99).

Table 1:

Baseline characteristics of the study population

	Overall	NfL tertiles		
		1	2	3
n	817	270	269	278
Demographics				
Age, years(SD)	80.7 (6.5)	77.6 (5.5)	80.6 (5.8)	83.8 (6.5)
Sex, men, n(%)	314 (38.4)	111 (41.1)	96 (35.7)	107 (38.5)
Race, African Americans, n (%)	482 (59.0)	195 (72.2)	150 (55.8)	137 (49.3)
Education, years (SD)	12.5 (3.5)	12.5 (3.4)	12.4 (3.5)	12.5 (3.8)
Vascular risk factors				
Current smoking, n (%)	67 (8.2)	33 (12.2)	22 (8.2)	12 (4.3)
Hypertension, n (%)	475 (58.1)	153 (56.7)	151 (56.1)	171 (61.5)
Diabetes, n (%)	195 (23.9)	54 (20.0)	62 (23.0)	79 (28.4)
Dyslipidemia, n (%)	188 (23.0)	59 (21.9)	68 (25.3)	61 (21.9)
Kidney function				
Creatinine, mg/dL	1.2 (0.7)	1.0 (0.3)	1.1 (0.3)	1.5 (1.1)
Cognitive function				
Global cognition, z-score	0.1 (0.8)	0.2 (0.6)	0.1 (0.7)	−0.1 (0.9)

Hypertension, diabetes, or dyslipidemia was based on self-reports or prescriptions for the condition-specific medication (e.g., statins)

Table 2:

Association of NfL with the risk of incident stroke

	Median of NfL, pg/mL	No. of Cases	Person-Years	HR	95% CI
Continuous	27.2	133	3603.1	1.28	1.1 – 1.5
Categorical					
T1	17.7	36	1413.7	1.00	reference
T2	27.1	48	1241.4	1.68	1.07 – 2.65
T3	48.1	49	948.0	2.35	1.45 – 3.81

Abbreviation: No., number of individuals with incident stroke; HR, hazard ratio; CI, confidence interval; Models are adjusted by age, sex, race, education, smoking, hypertension, diabetes, and dyslipidemia

Table 3:

Association of NfL with brain infarcts

	Median of NfL, pg/mL	N	% of People with Brain Infarcts	OR	95% CI
Continuous	25.6	470	25.5	1.32	1.06 – 1.66
Categorical					
T1	17.9	179	16.8	1.00	reference
T2	26.9	149	28.9	1.85	1.07 – 3.22
T3	47.8	142	33.1	2.03	1.14 – 3.66

Abbreviation: N, number of participants. Models are adjusted by age, sex, race, education, smoking, hypertension, diabetes, and dyslipidemia, and time from blood draw to MRI assessments