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Plasma total-tau as a biomarker of stroke risk in the community

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Abstract

Higher plasma total-tau level is associated with incident dementia but its relationship with stroke risk is unknown. In this prospective community-based study, we evaluated plasma total-tau level as a biomarker of stroke risk in 2794 Framingham Heart Study participants. Persons with plasma total-tau levels in the top quintile, versus the bottom four, had an increased risk of incident stroke over a mean follow-up of 8.3 years (Hazard Ratio, 2.01; 95% Confidence Interval, 1.32-3.08) following adjustments for age, sex, and stroke risk factors. Our findings demonstrate that plasma total-tau relates to the risk of stroke in a community sample.

Introduction

The tau protein is expressed in neurons and is involved in stabilizing microtubules and assisting with axonal maintenance and transport.¹ Damage to neurons may cause tau to leak into the cerebrospinal fluid and blood, whereby elevated total-tau (t-tau) levels act as a non-specific marker of neuronal injury.² We recently showed that higher plasma t-tau levels predicted the risk of incident dementia in the prospective, community-based Framingham

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Heart Study (FHS), with successful replication in the Memento Cohort.³ In that study, plasma t-tau was associated with the presence of both neurofibrillary tangles and microinfarcts at autopsy. We suspect that plasma t-tau levels may increase in response to brain injury from both vascular and neurodegenerative lesions predicting both stroke and dementia risk. Although we have demonstrated the latter,³ to our knowledge, plasma t-tau has not been examined with respect to the risk of incident stroke. Accordingly, we examined whether plasma t-tau associated with the risk of incident first-ever stroke in the community-based FHS.

Methods

Study sample

The FHS is an ongoing prospective community-based cohort in Massachusetts (USA). The study began in 1948 with the recruitment of an Original Cohort. Survivors have been followed prospectively with biennial examination cycles and ongoing surveillance for clinical events. In 1971, 5124 children of the Original cohort, as well as spouses of these children, were recruited into the Offspring Cohort. The Offspring Cohort has been studied across 9 examination cycles with detailed methods provided elsewhere.⁴ All participants provided written informed consent. The Institutional Review Board and Boston University Medical Center approved the study.

Assessment of plasma t-tau

Single Molecule Array (Simoa) technology permits the detection of t-tau from plasma with over 1000-fold improvement in sensitivity over conventional ELISA.^{5,6} At the eighth Offspring Cohort examination (2005-08), participants presented to the Heart Study clinic following an overnight fast. A blood draw was completed with samples immediately centrifuged, aliquoted and stored at -80°C . For this study, Quanterix (Lexington, MA) used these samples, which had never been thawed, to analyze plasma t-tau using a Simoa™ Tau 2.0 Kit and a Simoa HD-1 analyzer. This single-molecule digital ELISA is validated as fit-for-purpose research-use-only with a limit of detection at 0.019pg/mL. The assay detects all tau isoforms, including normal and phosphorylated tau. The analytical range was between 0.06 and 360pg/mL. The intra- and inter-assay coefficients of variation were 4.1% and 7.5%, respectively.

Stroke case ascertainment

Stroke incidence was assessed through the continuous monitoring of hospital admissions in Framingham and by reviewing all available medical records and results. We also asked participants about the occurrence of stroke and stroke symptoms at FHS examination cycle and during annual FHS health status updates. Where possible, a study neurologist visited participants suspected of having a stroke within 48 hours. Stroke was defined as focal neurological symptoms of rapid onset and presumed vascular origin, lasting >24 hours or resulting in death within 24 hours. A committee comprising of least three FHS investigators, including at least two neurologists, adjudicated stroke diagnosis. The committee considered all available medical records, brain imaging, cerebrovascular imaging, and the assessment of the study neurologist who visited the participant.

White Matter Hyperintensity Volume (WMHV)

WMHV was estimated from structural brain MRI with a combination of FLAIR and 3D-T1 images. Values were expressed as a percentage of intracranial volume and log transformed. Full methods are provided elsewhere.⁷

Statistical Methods

Our analysis sample was derived from persons who attended the 8th Offspring cohort examination cycle (N=3021) and had plasma t-tau measured (N=2885). We then excluded 13 participants aged under 45 years (since stroke in the young is rare), 71 persons with prevalent stroke, and 7 persons without stroke follow-up, leaving an analytical sample of 2794.

We related plasma t-tau to the risk of incident stroke using Cox Proportional Hazards regression models. Follow-up was from the baseline exam to the time of incident event, death, or date the participant was last known to be stroke-free, through to 2016. We adjusted results according to two statistical models. Model 1 included adjustments for age and sex. Model 2 included the addition of clinical stroke risk factors: systolic blood pressure, treatment for hypertension, current smoking status, total cholesterol, high density lipoprotein cholesterol, prevalent atrial fibrillation (noted by a Framingham cardiologist on any ECG done at or before the baseline examination), diabetes, and prevalent cardiovascular disease (CVD; coronary heart disease, myocardial infarction, intermittent claudication, congestive heart failure). Next, we examined the usefulness of plasma t-tau to predict the risk of incident stroke over and above the Framingham Stroke Risk Profile (FSRP). The FSRP uses an updated algorithm that estimates the 10-year risk of stroke using age, sex, current smoking status, prevalent CVD, prevalent atrial fibrillation, diabetes, hypertension treatment, and systolic blood pressure. The FSRP was validated in three large community cohorts.⁸ We examined whether plasma t-tau could improve risk stratification for incident stroke over and above the FSRP by calculating the continuous net reclassification improvement (NRI) applicable to survival data, taking into account events, non-events, and censoring.^{9,10} The 95% confidence interval (CI) was calculated using bootstrap methods.¹¹ The continuous NRI quantifies upward and downward movement as any change in predicted probabilities, with higher values indicating superior discrimination.¹⁰ All analyses were conducted using SAS V9.4 (SAS Institute, Cary, N.C.). Missing data were excluded from analysis. Results were deemed significant if $P < 0.05$ (two-tailed).

Results

Cohort characteristics

Persons with high plasma t-tau were also more likely to have prevalent CVD, atrial fibrillation, and diabetes and were more likely to receive treatment for high blood pressure (Table 1).

Plasma t-tau and the risk of incident stroke

We observed 101 (4%) cases of incident stroke over a mean follow-up of 8.3 ± 2.1 years, 82 were ischemic in origin. Plasma t-tau values were right skewed. We graphed the association

between each quintile of plasma t-tau levels and the risk of incident stroke adjusting for age and sex (Fig 1a). From these data, we observed a threshold effect at the level of the top quintile. Thus, for all analyses, we created a binary variable and examined plasma t-tau values in the top quintile ($> 4.95\text{pg/mL}$) versus the bottom 4. Persons with plasma t-tau in the top quintile displayed a greater than two-fold increase in the risk of stroke (Fig 1b, Table 2).

Sensitivity analysis

In a series of post-hoc sensitivity analyses (Table 2), we found similar effect sizes between plasma t-tau levels and stroke risk when excluding participants with prevalent dementia or other significant neurological diseases at baseline (e.g., multiple sclerosis), and when including additional adjustment for WMHV in a subsample with brain MRI. As compared with the primary analyses, we also found similar results when limiting the outcome to ischemic stroke, although attenuated slightly.

Plasma t-tau and the prediction of incident stroke

Persons with plasma t-tau in the top quintile, relative to the remainder of the sample, had a 2.28-fold increase in the risk of stroke following adjustment for the FSRP (HR, 2.28; 95% CI, 1.51-3.44). Adding plasma t-tau (at the threshold of the top quintile) to a model including the FSRP improved stroke risk discrimination (NRI overall, 0.47; 95% CI, 0.24-0.69; NRI events, -0.15 ; NRI non-events, 0.62).

Discussion

Our large study demonstrated that plasma t-tau associated with the risk of incident stroke in a community setting. A previous study of 50 acute ischemic stroke patients reported that plasma t-tau levels peaked 7 days post-stroke.¹² Moreover, higher plasma t-tau was related to greater stroke severity, poorer stroke outcomes, and larger infarct volumes. Thus, levels of plasma t-tau may increase in response to vascular brain injury and other brain insults. We extend the present literature to show that higher t-tau levels associate with the risk of first-ever stroke in a community sample.

In the FHS and other population-based cohorts, a higher burden of subclinical cerebrovascular disease is associated with a higher risk of incident stroke.^{13,14} Thus, t-tau may predict the risk of incident stroke through associations with subclinical vascular brain injury. Although associations between plasma t-tau and stroke remained following adjustment for WMHV, this imaging marker does not capture the full spectrum of vascular brain injury. For example, we have reported previously that higher plasma t-tau levels predict a higher burden of microinfarcts at autopsy as well as lower hippocampal volumes on brain MRI.³ In this study, we were underpowered to examine other imaging markers of vascular brain injury since MRI was only available on a subset.

Our study is not without limitations. Our findings are based on only 101 incident stroke cases, and our sample was mostly of European descent, meaning that it is unclear how our data will generalize to other ethnic groups. Our results will require replication in independent cohorts with different population attributes. Our study was observational meaning that we could not infer a causal relationship between increased t-tau levels and

incident stroke. As the t-tau assay is relatively new, the reproducibility of plasma t-tau within individuals and the comparability of values across different populations need further study. Future studies are needed to refine the thresholds most predictive of future stroke across populations and settings.

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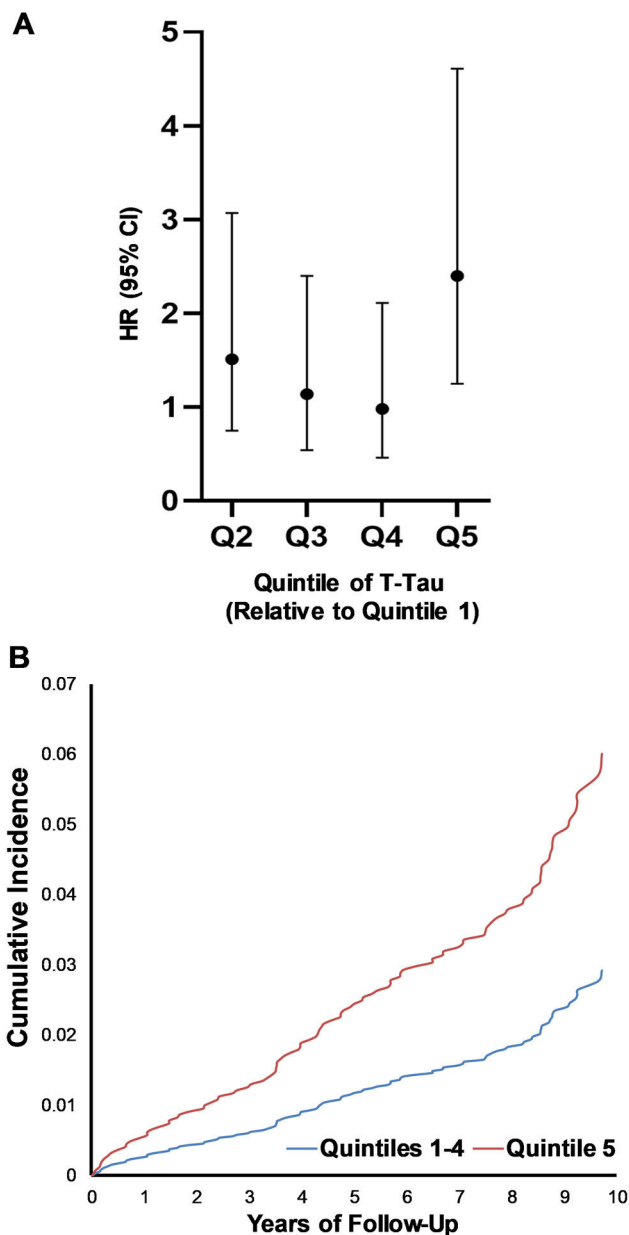


Figure 1. Risk of incident stroke for each quintile of plasma t-tau, relative to quintile one (A), and the adjusted cumulative incidence of stroke by quintile five of plasma t-tau, versus quintiles 1-4 (B).

Data are for the incidence of all-cause stroke, adjusting for age and sex. The plasma t-tau values that define each quintile (in pg/mL) are: Q1, 0.12-3.02; Q2, >3.02-3.58; Q3, >3.58-4.14; Q4, >4.14-4.95; Q5, >4.95-106.75). The linear relationship between the log of plasma t-tau (per standard deviation unit increase) and the incidence of all-stroke was HR, 1.28 (95 % CI, 1.05, 1.54) following adjustments for age and sex (Model 1) and HR, 1.22

(95% CI, 1.01, 1.49) following additional adjustments for stroke risk factors (Model 2). CI = confidence interval, HR = Hazard ratio, Q = quintile, T-Tau = plasma total=tau.

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Table 1.

Cohort characteristics

Characteristic	Plasma t-tau threshold		
	Q1-4	Q5	Overall
No. of subjects	2235	559	2794
Age, yr	66±9	70±9	67±9
Male, No. (%)	1094 (49)	179 (32)	1273 (46)
Total cholesterol, mg/dL	187±37	181±38	186±37
HDL cholesterol, mg/dL	58±18	57±18	58±18
Body mass index, kg/m ²	28±5	29±6	28±5
Current smoker, No. (%)	199 (9)	46 (8)	245 (9)
Systolic blood pressure, mmHg	128±17	131±19	129±17
Treatment for blood pressure, No. (%)	1124 (50)	364 (65)	1488 (53)
Prevalent diabetes mellitus, No. (%)	293 (13)	123 (23)	416 (15)
Prevalent CVD, No. (%)	268 (12)	130 (23)	398 (14)
APOE ε4, No. (%) ^a	478 (22)	124 (23)	602 (22)
Prevalent atrial fibrillation, No. (%)	132 (6)	62 (11)	194 (7)
FSRP ^b , score units	0.07±0.07	0.1±0.1	0.07±0.08
Stroke follow-up, years	8.4±2.0	7.8±2.3	8.3±2.1
White matter hyperintensity volume, % ^c , median (Q1, Q3)	0.17 (0.10, 0.34)	0.24 (0.11, 0.46)	0.18 (0.10, 0.36)

CVD = cardiovascular disease; FSRP = Framingham Stroke Risk Profile; HDL = high-density lipoprotein; Q1, Q3 = quartile 1, quartile 3. The threshold for the plasma t-tau top quintile was 4.95pg/mL. Data are mean ± standard deviation unless stated otherwise.

^aPositive for at least one APOE ε4 allele.

^bEstimates the 10-year risk of stroke in persons free of stroke by assigning points based on a persons risk factor profile.

^cAvailable for a subset of 1581 persons with brain MRI. The overall median (quartile 1, quartile 3) level of plasma t-tau was 3.85 pg/mL (3.16, 4.71).

Table 2.

Plasma t-tau and the risk of incident stroke

Model and plasma t-tau criterion	No. of Events/ No. at Risk	Stroke Risk	
		HR (95% CI)	P Value
Risk of all-stroke in Model 1^a			
Q5 ^b	40/559	2.09 (1.38, 3.17)	0.0005
Q1-4	61/2235	Reference	-
Risk of all-stroke in Model 2^c			
Q5 ^b	40/541	2.01 (1.32, 3.08)	0.001
Q1-4	60/2170	Reference	-
Sensitivity analysis 1^d			
Q5 ^b	31/553	2.03 (1.27, 3.25)	0.003
Q1-4	49/2211	Reference	-
Sensitivity analysis 2^e			
Q5 ^b	39/545	2.10 (1.38, 3.20)	0.0006
Q1-4	59/2134	Reference	-
Sensitivity analysis 3^f			
Q5 ^b	17/312	2.00 (1.08, 3.71)	0.03
Q1-4	30/1269	Reference	-

^aAdjusts for age and sex.

^bThreshold corresponds to the top quintile (Q5) with respect to the remainder of the sample (Q1-4).

^cAdjusts for age, sex, systolic blood pressure, treatment for hypertension, current smoking status, total cholesterol, High-density lipoprotein cholesterol, prevalent atrial fibrillation, diabetes, and cardiovascular disease.

^dRisk of ischemic stroke, adjusting for Model 1 covariates.

^eRisk of all-stroke excluding persons with prevalent dementia or other significant neurological disease at baseline, adjusting for Model 1 covariates.

^fRisk of all-stroke after adjusting for white matter hyperintensity burden and Model 1 covariates. Based on a subsample of the larger cohort with brain MRI.

CI = confidence interval, HR = hazard ratio, Q= quintile, SD = standard deviation.