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RESEARCH

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Plasma A β and neurofilament light chain are associated with cognitive and physical function decline in non-dementia older adults

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Abstract

Background: Cognition is closely associated with physical function. Although high brain amyloid- β (A β) deposition and neurofilament light chain (NfL) are associated with cognitive and gait speed decline, relationships of combined plasma A β and NfL profiles with cognitive and physical functions in older adults remain unknown. The research aim of this study was to investigate the prospective associations of combined plasma A β and NfL profiles with cognitive and physical functions in older adults.

Methods: Participants ($n = 452$, aged 76 ± 5 years) who had both plasma A β and NfL data collected from the Multidomain Alzheimer's Preventive Trial (MAPT, May 2008 to April 2016) were included in the current study. These participants were from four MAPT groups (multidomain interventions [physical activity and nutritional counselling, and cognitive training], omega-3 supplementation, multidomain plus omega-3 supplementation and control group) and had received a 3-year intervention, followed by a 2-year observational follow-up. Cognitive function was evaluated as Mini-Mental State Examination and composite cognitive score (CCS, a mean Z-score combining four cognitive tests). Physical function was evaluated as gait speed (4-m usual-pace walk test) and chair-stand time (5-time maximal chair-stand test). Cognitive and physical function data measured at the time of and after blood A β and NfL tests were used for analysis. Participants with plasma A β_{42} /A β_{40} ratios lower than 0.107 and NfL levels greater than 93.04 pg/ml were classified as A β + and NfL+. Multivariable regressions and mixed-effects linear models were used for the analysis.

Results: At the cross-sectional level, no significant association was found between A β +NfL+ and cognitive or physical function after controlling for age, sex, body mass index, education level and MAPT group. Evaluating longitudinal changes, participants with A β +NfL+ had greater annual declines in the CCS ($\beta = -0.11$, 95%CI [-0.17, -0.05]) and gait speed ($\beta = -0.03$, 95%CI [-0.05, -0.005]). After adjusting for APOE $\epsilon 4$ genotype, A β +NfL+ was associated with a greater decline only in the CCS ($\beta = -0.09$, 95%CI [-0.15, -0.02]).

(Continued on next page)

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Conclusions: Combined low plasma $A\beta_{42}/A\beta_{40}$ ratio and high plasma NfL level was associated with greater declines in cognition and gait speed over time, providing further evidence of the links between cognitive and physical function.

Trial registration: www.clinicaltrials.gov [NCT00672685].

Keywords: Amyloid- β , Neurofilament light chain, Cognitive function, Physical function

Background

Decreased physical function has been associated with cognitive impairment in older adults [1, 2]. Multiple studies have examined the association between physical function and brain biomarkers of neurodegeneration, such as amyloid- β ($A\beta$) and neurofilament light chain (NfL). Higher brain $A\beta$ burden, cerebrospinal fluid (CSF) $A\beta_{42}/A\beta_{40}$ ratio and NfL levels are associated with slower gait speed [3–5] and greater gait variability [6]. Yet, no association was found with chair-stand [7]. Considering the close connection between brain and plasma biomarkers, it is plausible to think that plasma $A\beta$ and NfL concentrations might also be associated with physical function. However, no study has been performed to examine this association in an older population. Meanwhile, a recent research by de Wolf et al. [8] has reported that adults with both low plasma $A\beta_{42}$ and high NfL levels demonstrated a higher risk of developing dementia or AD than those with one biomarker condition (i.e. low $A\beta_{42}$ or high NfL). Therefore, a combined plasma $A\beta$ and NfL condition might be associated with declines in both cognitive and physical functions. The objective of this study is to explore the possible association between combined plasma $A\beta$ and NfL condition with the evolution of physical function in older adults.

Methods

The Multidomain Alzheimer's Preventive Trial (MAPT, ClinicalTrials.gov [NCT00672685]) was a randomized, controlled trial that compared multidomain interventions (physical activity and nutritional counselling and cognitive training) and omega-3 supplementation, combined or alone, with a placebo control group [9]; no effects of the MAPT interventions on cognitive function and gait speed over a 3-year period were found [10]. MAPT was approved by the ethics committee in Toulouse (CPP SOOM II). Written consent forms were obtained from all participants.

Study population

Older adults (70 years or over) with spontaneous memory complaints or limitations in at least one instrumental activity of daily living or a gait speed lower than 0.8 m/s were recruited in the MAPT. Our current study included

452 participants who had available information on plasma $A\beta$ and NfL levels.

Evaluation of cognitive and physical functions

Cognitive function was evaluated as Mini-Mental State Examination (MMSE, ranging from 0 to 30, higher is better) and composite cognitive score (CCS), which was calculated as a mean Z-score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding Test, ten MMSE orientation items, the Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale–Revised and the Category Naming Test) [10]. Physical function was evaluated as gait speed, which was measured by a 4-m usual-pace walk test (m/s), and chair-stand time (s), which was measured by a 5-repetition maximal speed chair-stand test. Outcome measures were evaluated at baseline, the 6th month and each year during the 3-year intervention period and the 2-year observational follow-up. Data of outcome measures collected at the same time point and after blood tests were used in this study.

Measurement of plasma $A\beta$ and NfL levels

Plasma $A\beta_{42}$ and $A\beta_{40}$ levels were assessed by immunoprecipitation mass spectrometry as previously described [11]. $A\beta$ levels were analysed and calculated by integrated peak area ratios to known concentrations of the internal standards using the Skyline software package [12]. Plasma NfL levels were measured using the R-PLEX human neurofilament L antibody set (Meso Scale Discovery, F217X). Samples were diluted 2-fold in a diluent buffer and tested in duplicate according to the manufacturer's instructions.

Plasma $A\beta$ or NfL levels were measured once using blood samples collected in the first or second year of the study. For most participants ($n = 420$ out of 452), $A\beta$ and NfL levels were measured from blood samples taken at the 1-year wave of data collection. For the rest of the participants, plasma markers were measured using samples from the second year. Blood samples were collected on the same day as cognitive and physical function evaluation.

Plasma $A\beta_{42}/A\beta_{40}$ ratio and NfL stratification

The selection of $A\beta_{42}/A\beta_{40}$ ratio cut-off value was performed based on participants ($n = 201$) who underwent

amyloid [¹⁸F] florbetapir positron emission tomography (PET positive when standardized uptake value ratios ≥ 1.17) [13] using logistic regression (PET positive/negative as the dependent variable and Aβ₄₂/Aβ₄₀ as the independent variable) with Youden's Index as the metric (higher is better) [11]. The cut-off value of NfL was determined as the upper quartile of our participants. Participants with low Aβ₄₂/Aβ₄₀ ratios (≤ 0.107) and high NfL levels (≥ 93.04 pg/ml) were classified as Aβ+NfL+.

Covariates

Age, sex, body mass index (kg/m²), education level and MAPT group. Since almost 10% of the participants did not have APOE ε4 genotype data, separate models were performed with and without APOE ε4 genotype (dichotomous variable) as an additional covariate.

Statistics

Descriptive data was presented as mean ± standard deviation (SD) or absolute numbers with percentage, as appropriate. Comparisons between the Aβ+NfL+ group and the rest of the population were performed with Student's *t* test and chi-square test, as appropriate.

Multivariable linear regression was used for cross-sectional analyses with cognitive or physical functions (separate models) measured at the moment of the blood test as dependent variables and Aβ+NfL+ as the independent variable of interest. Longitudinal analyses were performed using separated mixed-effects linear models with longitudinal data of cognitive or physical functions

as dependent variables. A random effect at the participant level and a random slope of time were assumed. All analyses were controlled for the covariates mentioned above and were performed using SAS 9.4. *p* values were corrected for multiple testing by Benjamini–Hochberg procedure [14], with a significance level of 0.05, in cross-sectional and longitudinal models with and without APOE ε4 genotype, separately.

Results

The characteristics of the participants are presented in Table 1. The average age of our participants was 76 years, and 59% of the participants were female. ninety-three per cent of the participants had plasma biomarkers tested from blood samples collected 1 year after the enrolment of the MAPT. Participants with plasma Aβ+NfL+ were older and had lower CCS than the other participants.

The cross-sectional analysis did not show any significant association between plasma Aβ+NfL+ and cognitive or physical function after controlling for covariates (Table 2).

Longitudinal analysis showed that participants with plasma Aβ+NfL+ had greater declines in CCS and gait speed over time. After adjusting for APOE ε4 genotype, Aβ+NfL+ was still associated with greater declines in CCS while no significance in gait speed was found (Table 3). No significant associations were found between Aβ+NfL+ status and MMSE or chair-stand. For the covariates, the MAPT intervention groups were not significantly associated with cognitive or physical functions.

Table 1 Characteristics of participants in this study

Parameters	All participants			Participants with APOE genotype data		
	Total (n = 452)	Aβ+NfL+ group (n = 46)	Other participants [†] (n = 406)	Total (n = 410)	Aβ+NfL+ group (n = 39)	Other participants [†] (n = 371)
Age (year), mean (SD)	76 (5)	78 (5)**	76 (5)	76 (5)	78 (5)**	76 (5)
Female, n (%)	268 (59%)	23 (50%)	245 (60%)	224 (55%)	19 (49%)	224 (60%)
Participants with plasma biomarkers measured in the first year, n (%)	420 (93%)	44 (96%)	376 (93%)	382 (93%)	37 (95%)	345 (93%)
Initial body mass index, mean (SD)	26.4 (4.0)	25.9 (3.8)	26.5 (3.9)	26.4 (3.8)	25.6 (3.1)	26.5 (3.9)
Initial CCS, mean (SD)	0.07 (0.79)	- 0.25 (0.70)**	0.10 (0.79)	0.10 (0.77)	- 0.20 (0.71)*	0.14 (0.78)
Initial MMSE, mean (SD)	27.8 (1.9)	27.5 (1.7)	27.9 (1.9)	27.9 (1.8)	27.7 (1.6)	27.9 (1.8)
Initial gait speed (m/s), mean (SD)	1.0 (0.2)	1.0 (0.3)	1.0 (0.2)	1.0 (0.2)	1.0 (0.3)	1.0 (0.2)
Initial chair-stand time (s), mean (SD)	12.1 (4.3)	12.9 (4.0)	12.0 (4.4)	12.0 (4.3)	12.9 (4.2)	11.9 (4.3)
Aβ ₄₂ /Aβ ₄₀ ratio, mean (SD)	0.114 (0.018)	0.097 (0.010)**	0.116 (0.018)	0.113 (0.018)	0.096 (0.010)**	0.115 (0.018)
NfL (pg/ml), mean (SD)	86.65 (74.09)	160.35 (137.01)**	78.30 (57.79)	85.70 (75.50)	162.55 (143.15)**	77.62 (59.23)

p* < 0.05, *p* < 0.01 when compared Aβ+NfL+ group with other participants

[†]Other participants without Aβ+NfL+ condition

Table 2 Multivariable linear regression of cognitive and physical functions by Aβ+NfL+ conditions

Parameters	Aβ+NfL+ group (all participants) [#]				Aβ+NfL+ group (with APOE) [#]			
	Coefficient	p	Adjusted p ^Δ	95%CI	Coefficient	p	Adjusted p ^Δ	95%CI
Initial CCS	-0.19	0.11	0.45	(-0.42, 0.04)	-0.15	0.24	0.85	(-0.39, 0.10)
Initial MMSE	-0.02	0.93	0.93	(-0.60, 0.55)	-0.03	0.92	0.92	(-0.57, 0.64)
Initial gait speed (m/s)	-0.01	0.87	0.93	(-0.08, 0.07)	-0.02	0.63	0.85	(-0.10, 0.06)
Initial chair-stand time (s)	0.34	0.61	0.93	(-1.00, 1.69)	0.50	0.50	0.85	(-0.95, 1.94)

Covariates: age, sex, body mass index, education level and MAPT group

[#]Participants without Aβ+NfL+ condition as the reference

^Δp value adjusted by Benjamini–Hochberg procedure

Discussion

This study focused on the association between the combined plasma Aβ and NfL condition and cognitive and physical functions in older adults over a nearly 4-year period. We report for the first time that older adults with combined low plasma Aβ₄₂/Aβ₄₀ ratios and high NfL levels had more declines in cognitive (detected in CCS but not MMSE) and physical functions (detected in gait speed but not chair rise) over time while no cross-sectional association was found. Such findings indicate the feasibility of using plasma biomarkers to estimate the progressive decline of cognitive and physical functions in older adults over time.

Previous studies have reported the association between cognition and each of the biomarkers analysed in our research. Yaffe [15] analysed the baseline plasma Aβ₄₂/Aβ₄₀ ratio and a 10-year longitudinal cognition data in older adults (average age of 74 years) and reported that lower Aβ₄₂/Aβ₄₀ ratio was associated with greater cognitive decline. A similar longitudinal association between plasma NfL and cognition was also found in the study of Mielke et al. [16], who analysed the cognition data over a 15- or 30-month period in older adults with a median age of 76 years. Notably, no cross-sectional association between plasma biomarkers and cognition was found in both studies mentioned above. Our results based on combined plasma Aβ and NfL condition further confirmed these cross-sectional and longitudinal associations. Moreover, our findings are consistent with previous studies which reported that greater longitudinal cognitive declines were associated with higher plasma NfL levels in older adults with abnormal brain Aβ

conditions (e.g. low CSF Aβ and high brain Aβ deposition) [17, 18].

Additionally, we further extend the literature by showing that the plasma Aβ+NfL+ profile was associated with the longitudinal decline of gait speed, but not chair-stand. These results are in line with our previous findings (based on the same MAPT dataset) about brain Aβ deposition and physical function, which reported that greater brain Aβ burden was associated with lower gait speed [3], but not chair rise [7]. Other researchers have also reported that high CSF Aβ₄₂/Aβ₄₀ ratio, NfL level and Aβ burden in the brain subregions were associated with increased gait variability [6] and low gait speed [4, 5], while similar studies for plasma Aβ and NfL are lacking. The difference in associations between gait speed and chair-stand with the plasma biomarkers in our study might be related to the various mechanisms behind those two physical functions. Chair-stand performance is more dependent on lower limb muscle function (strength and power) than gait speed; the latter is a more complex movement which involves dynamic balance control, coordination and muscle function. The significant association between plasma biomarkers and gait speed, but not chair-stand, indicates that these neurodegeneration-related biomarkers might be connected with the neural aspect of gait speed, such as cognitive status [19], motor control [20] and muscle synergies [21]. Since plasma NfL is closely associated with axonal damage [22] and plasma Aβ is associated with CSF Aβ [23], which is involved in synaptic function and multiple signalling pathways (e.g. calcium signalling and insulin-like growth factor-I signalling) [24], the less

Table 3 Mixed-effects linear models of cognitive and physical functions by Aβ+NfL+ conditions

Parameters	Aβ+NfL+ group × time (all participants) [#]				Aβ+NfL+ group × time (with APOE) [#]			
	Coefficient	p	Adjusted p ^Δ	95%CI	Coefficient	p	Adjusted p ^Δ	95%CI
CCS	-0.11	0.0004	0.002	(-0.17, -0.05)	-0.09	0.007	0.03	(-0.15, -0.02)
MMSE	-0.14	0.18	0.24	(-0.34, 0.06)	-0.06	0.55	0.74	(-0.27, 0.14)
Gait speed (m/s)	-0.03	0.02	0.04	(-0.05, -0.005)	-0.02	0.08	0.17	(-0.05, 0.003)
Chair-stand time (s)	0.08	0.66	0.66	(-0.28, 0.44)	-0.001	0.99	0.99	(-0.38, 0.38)

Covariates: age, sex, body mass index, education level and MAPT group

[#]Participants without Aβ+NfL+ condition as the reference

^Δp value adjusted by Benjamini–Hochberg procedure

favourable plasma NfL and A β condition (i.e. A β +NfL+) might suggest structural and functional changes in the nervous system at a fundamental level. Consequently, besides cognitive degeneration, structural and functional changes in motor-related brain regions and peripheral neural pathways might also lead to gait speed decline. Therefore, further studies are still needed to explore the association between plasma biomarkers and the structural or functional changes in the central and peripheral nervous systems.

Notably, although A β +NfL+ was associated with gait speed decline, such decline has not reached the clinically meaningful threshold of 0.05 m/s [25]. Further studies are also needed to examine if the cognitive decline in CCS is clinically meaningful.

Our study only examined the initial plasma A β and NfL combined condition with cognitive and physical functions while previous studies have demonstrated the close associations between overtime biomarker changes and changes in cognitive performance. A 10-year follow-up study by Okereke et al. [26] on late middle-aged adults (average age of 64 years) reported that with a 1 SD (standard deviation) increase in the change of plasma A β_{40} /A β_{42} ratio, there was a 0.02-unit/year more decline in global cognitive score. A recent study by Mattson et al. [27] has shown that increased plasma NfL levels over time were associated with larger global cognitive decline. Yet, the association between longitudinal biomarker changes and physical function remains to be established and needs further exploration.

Limitation

We analysed data from a randomized controlled trial. Although there are no significant differences in plasma A β_{42} /A β_{40} ratios and NfL levels among the MAPT groups, the MAPT interventions might affect plasma A β and NfL levels which were tested based on blood samples collected at the first/second year of the study. Therefore, it would be more appropriate if observational data were used. Since the longitudinal biomarker data were not available in our study, we could not confirm if there was any change in the combined A β and NfL status over the 4-year period. Moreover, the absence of longitudinal data of the biomarkers impeded us from looking at the association between changes in biomarkers and changes in cognitive and physical functions.

Conclusions

Our results suggest the possibility of using easily accessible plasma A β_{42} /A β_{40} ratio and NfL profiles as combined biomarkers to estimate declines in cognition and gait speed over time. Further studies on other cohorts are still needed to examine the reliability of the plasma biomarker cut-off values (identified in this study) for the classification of A β +NfL+ status. Based on the combined

plasma A β +NfL+ status, the incidence of neurological disorders, such as dementia and AD, can be further studied. Moreover, the association between A β +NfL+ status and the structural changes of motor-related brain regions can be examined to understand if the physical function changes found in our study is related to changes in motor-related central nervous system.

Abbreviations

A β : Amyloid- β ; CCS: Composite cognitive score; MAPT: Multidomain Alzheimer's Preventive Trial; MMSE: Mini-Mental State Examination; NfL: Neurofilament light chain; PET: Positron emission tomography

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Authors' contributions

LH analysed and interpreted the data and was a major contributor in writing the manuscript. PSB interpreted the data and revised the manuscript for intellectual content. GA, ADN and JEM are members of the NFL testing team and revised the manuscript for intellectual content. YL and RJB are members of the A β testing team and revised the manuscript for intellectual content. BV revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Authors' information

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The MAPT was approved by the ethics committee in Toulouse (CPP SOOM II). Written consent forms were obtained from all participants.

Consent for publication

Participants consented for the publication.

Competing interests

The authors declare that they have no competing interests.

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