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Pre-Existing Frailty is Unrelated to Progression of Diffuse Subcortical Damage of Vascular Origin: A Longitudinal Prospective Study in Community-Dwelling Older Adults

Oscar H. Del Brutto[1,2], Bettsy Y. Recalde[1], Denisse A. Rumbea[1], and Robertino M. Mera[3]

Abstract

Background: Both frailty and white matter hyperintensities (WMH) of presumed vascular origin are associated with enhanced expression of inflammatory biomarkers. Therefore, it is possible that pre-existing frailty predisposes to WMH progression. However, this relationship has not been explored. This population-based longitudinal prospective study aimed to assess the impact of frailty on subsequent progression of WMH in community-dwelling older adults living in rural Ecuador. **Methods:** Participants of the Atahualpa Project Cohort received baseline frailty assessment and brain MRIs. Frailty was evaluated by means of the Edmonton Frail Scale (EFS). WMH were graded according to the modified Fazekas scale. Individuals who received a follow-up brain MRI were included. Poisson regression models were fitted to assess the differential rate of WMH progression according to EFS score, after adjusting for demographics, level of education, and cardiovascular risk factors. **Results:** The study included 263 individuals aged ≥60 years (mean age: 65.7 ± 6.2 years; 57% women). The mean EFS score at baseline was 4 ± 2.3 points. Follow-up MRIs after a median follow-up of 6.5 years showed WMH progression in 103 (39%) individuals. The EFS score at baseline was associated with WMH progression in unadjusted analysis ($P = .006$). However, significance was not achieved in a multivariate Poisson regression model adjusted for relevant covariates (IRR: 1.07; 95% C.I.: 0.97-1.18; $P = .192$). **Conclusions:** Study results do not support an independent relationship between frailty and WMH progression, adjusting for the confounding effect of aging.

Keywords

frailty, white matter hyperintensities, cerebral small vessel disease, older adults, population-based study

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Introduction

Frailty is a geriatric condition characterized by reduced functional reserve and vulnerability that is often associated with cognitive impairment in the absence of dementia.[1-3] This condition has been linked to several adverse outcomes, including the development of systemic and cardiovascular diseases, increased risk of hospitalization, institutionalization, and all-cause mortality.[4-6] In addition, some cross-sectional studies have evaluated the potential association between frailty and neuroimaging evidence of diffuse subcortical vascular damage, also known as white matter hyperintensities (WMH) of presumed vascular origin,[7-10] and some others have found a longitudinal relationship between the presence of this neuroimaging biomarker of cerebral small vessel disease (cSVD) and frailty progression in the follow-up.[11,12] In as much as this relationship is biologically plausible since both (frailty and cSVD) are

[1]Universidad Espíritu Santo-Ecuador, Samborondón, Ecuador
[2]Hospital-Clínica Kennedy, Samborondón, Ecuador
[3]Biostatistics/Epidemiology, Freenome, Inc., South San Francisco, CA, USA

Corresponding Author:
Oscar H. Del Brutto, School of Medicine and Research Center, Universidad Espíritu Santo-Ecuador, Urbanización Toscana, Apt 3H, Km 4.5 vía Puntilla-Samborondón 092301, Samborondón-Ecuador.
Email: oscardelbrutto@hotmail.com.

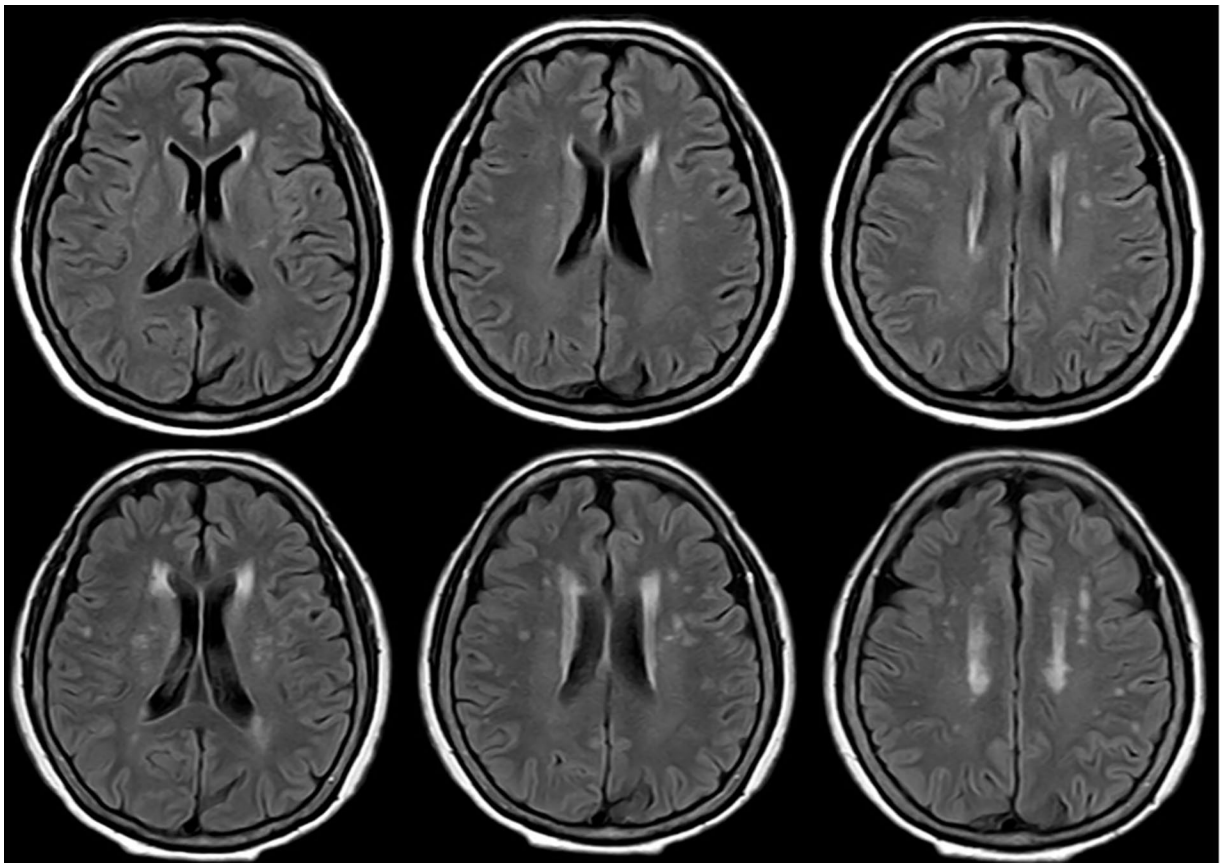

Figure 1. Fluid-attenuated inversion recovery MRI of a 65 year-old man showing progression of white matter hyperintensities from baseline MRI (upper row) performed in August 2014, to follow-up MRI (lower row) performed in July 2021.

associated with enhanced expression of inflammatory biomarkers,[13-15] it is also possible that pre-existing frailty predisposes to WMH progression. In this view, it has been demonstrated that WMH may occur in otherwise healthy subjects and that traditional risk factors only partially explain development or progression of this biomarker of cSVD, hence the need of investigating non-traditional risk factors that may be associated to WMH progression.[16] To the best of our knowledge, however, the relationship between pre-existing frailty and the subsequent progression of WMH has not been explored thus far. This population-based longitudinal prospective study aimed to assess the impact of frailty on subsequent progression of diffuse subcortical damage of vascular origin in community-dwelling older adults living in rural Ecuador.

Material and Methods

Study Population and Design

The study was conducted in Atahualpa, an isolated village where previous studies on frailty correlates have been carried out.[17,18] Characteristics of the village and its population have previously been detailed.[19] As noticed, Atahualpa residents are homogeneous regarding race/ethnicity, socio-economic status, lifestyles, and dietary habits.

Following a longitudinal prospective design, individuals aged ≥60 years enrolled in the Atahualpa Project Cohort who had a baseline MRI of the brain, evaluation of cardiovascular risk factors, and frailty assessment between 2012 and 2019 were considered eligible, and those who were actively participating as of May 2021 and received follow-up MRIs were included. Study participants have been identified by means of door-to-door surveys and have signed a comprehensive informed consent at enrollment and before the follow-up MRIs. The study was approved by the I.R.B. of our Institution. WMH progression was evaluated according to the EFS at baseline, after adjusting for relevant confounders (see below).

Frailty Assessment

Frailty was evaluated by means of the Edmonton Frail Scale (EFS), a validated field instrument that consists of 10

domains with 11 items including cognition, general health status, functional independence, social support, medication use, nutrition, mood, and balance and mobility.[20] The maximum EFS is 17 points, with higher scores corresponding to greater frailty levels.

Neuroimaging Studies

Both baseline and follow-up MRIs were performed with the same equipment and protocols (Philips Intera 1.5T; Philips Medical Systems, Eindhoven, the Netherlands). Interest focused on the presence and severity of WMHs. These lesions appear hyperintense on T2-weighted images that remained bright on FLAIR (without cavitation). WMH were graded as mild, moderate, and severe according to the modified Fazekas scale.[21] Accordingly, the presence of periventricular caps or thin lesions and punctate hyperintensities in subcortical white matter were rated as mild WMH, the presence of a smooth periventricular halo and subcortical foci that begin to merge as moderate WMH, and extension of periventricular lesions into the subcortical white matter and visualization of large confluent subcortical foci as severe WMH. Both, baseline and follow-up MRIs were read by 1 neuroradiologist and 1 neurologist blinded to clinical information. Kappa coefficients for interrater agreement of WMH severity were higher than .90 (at baseline and follow-up); discrepancies were resolved by consensus. WMH progression was defined as the increase in at least 1 grade of the Fazekas scale in the follow-up MRI (Figure 1).

Covariates Investigated

Demographics, level of education, and traditional cardiovascular risk factors were recorded at the time of baseline MRI. Interviews and procedures for measuring cardiovascular health (CVH) metrics followed the recommendations of the American Heart Association (AHA), which stratifies each of these metrics in the poor range according to well-defined cutoffs, as follows: (1) Poor smoking status if the subject is a current smoker or quitted <1 year; (2) Poor body mass index if $\geq 30\,kg/m^2$; (3) Poor physical activity if there is no moderate and vigorous activity; (4) Poor diet if there is none or only one of AHA proposed healthy components; (5) Poor blood pressure if $\geq 140/90$ mmHg; (6) Poor fasting glucose if ≥ 126 mg/dL; and (7) Poor total cholesterol blood levels if ≥ 240 mg/dL.[22]

Statistical Analysis

Continuous variables were compared by linear models and categorical variables by the chi-square or Fisher exact test in univariate analyses. To calculate person-years of follow-up, we considered the time from baseline to follow-up MRIs, which was variable enough to require a time to event analysis. Poisson regression models were fitted in order to estimate the incidence rate ratio (IRR) of WMH progression over time according to the baseline EFS score, after adjusting for the above-mentioned covariates. These models took into account the effect of time on WMH progression according to frailty severity at baseline. All data analyses were carried out by using STATA version 17 (College Station, TX, USA).

Results

Of 478 individuals aged ≥ 60 years enrolled in the Atahualpa Project cohort, 403 (84%) received a baseline brain MRI, clinical interviews, and frailty assessment. Among the 75 excluded individuals, 36 died or emigrated before the MRI, 19 did not accept to participate, 17 were severely disabled or had contraindications for MRI, and 3 had incomplete clinical information. Of 403 eligible candidates, 263 (65%) had a follow-up brain MRI and were included in the study (and utilized in the analysis). Of the 140 non-included participants, 90 died, and the remaining 50 either declined further consent, became disabled over the study years, or emigrated between baseline and follow-up MRI. Follow-up time between baseline and follow-up MRIs was 1711 person-years (95% C.I.: 1665-1757 years), and the median follow-up was 6.5 years (interquartile range: 2.3-7.8 years).

The mean age of 263 study participants was 65.7 ± 6.2 years (median age: 63.9 years) at baseline, 149 (57%) were women, and 192 (73%) had primary school education only. CVH metrics in the poor range included: smoking status: 11 (4%); body mass index: 63 (24%); physical activity: 12 (5%); diet: 11 (4%); blood pressure: 104 (40%); fasting glucose: 72 (27%); and total cholesterol blood levels: 41 (16%). The mean EFS score was 4 ± 2.3 points (median score: 4 points).

On baseline MRI, 90 (34%) participants did not have WMH, 131 (50%) had mild, 33 (13%) had moderate, and 9 (3%) had severe WMH. At follow-up, 52 (20%) individuals did not have WMH, 112 (43%) had mild, 67 (25%) had moderate, and 32 (12%) had severe WMH. Overall, 103 (39%) individuals had MRI evidence of WMH progression. Progression from none-to-mild WMH was noticed in 33 cases, from none-to-moderate in five, from mild-to-moderate in 42, from mild-to-severe in 10, and from moderate-to-severe in 13.

In unadjusted analysis, the mean value of the continuous EFS score was significantly higher among individuals who had WMH progression (4.5 ± 2.4 vs 3.7 ± 2.2; $P = .006$). Regarding the investigated covariates, people who had WMH progression were older ($P < .001$) and were less often obese ($P = .023$) than those who did not; otherwise, there were no significant differences in clinical characteristics across groups (Table 1).

Table 1. Characteristics of Atahualpa Residents Aged ≥60 Years According to Categories of White Matter Hyperintensities (WMH) Progression (Unadjusted Analysis).

	No progression of WMH (n = 160)	Progression of WMH (n = 103)	*P* value
Edmonton Frail Scale score, mean ± SD	3.7 ± 2.2	4.5 ± 2.4	.006*
Age at baseline, years, mean ± SD	64.3 ± 5.8	67.9 ± 6	<.001*
Women, n (%)	91 (57)	58 (56)	.928
Primary school education, n (%)	112 (70)	80 (78)	.171
Current smoker, n (%)	11 (7)	0	. . .
Body mass index ≥ 30 kg/m^2, n (%)	46 (29)	17 (17)	.023*
Physical inactivity, n (%)	9 (6)	3 (3)	.304
Unhealthy diet, n (%)	7 (4)	4 (4)	.846
Blood pressure ≥ 140/90 mmHg	60 (38)	44 (43)	.389
Fasting glucose ≥ 126 mg/dL	45 (28)	27 (26)	.757
Total cholesterol ≥ 240 mg/dL	26 (16)	15 (15)	.713

*Statistically significant result.

Table 2. Poisson Regression Model Showing That the Incidence Rate Ratio (IRR) of White Matter Hyperintensities (WMH) Progression is Not Associated With the Edmonton Frail Scale at Baseline.

WMH progression	IRR	95% C.I.	*P* value
Edmonton Frail Scale (points)	1.07	0.97-1.18	.192
Age at baseline	1.03	0.99-1.06	.101
Being female	0.87	0.56-1.35	.538
Primary school education	1.06	0.65-1.72	.812
Body mass index ≥ 30 kg/m2	0.73	0.42-1.29	.280
Poor physical activity	0.72	0.22-2.37	.594
Poor diet	0.93	0.33-2.59	.886
Blood pressure ≥ 140/90 mmHg	0.98	0.64-1.48	.916
Fasting glucose ≥ 126 mg/dL	0.93	0.59-1.46	.756
Total cholesterol ≥ 240 mg/dL	0.90	0.51-1.60	.730

An univariate Poisson regression model, only taking into account the effect of time between baseline and follow-up MRI, revealed a marginal significance in the relationship between the EFS score at baseline and WMH progression at follow-up (IRR: 1.07; 95% C.I.: 0.99-1.16; P = .086). Then, a fully-adjusted Poisson regression model showed no association between baseline EFS scores (used as a continuous independent variable) and WMH progression (IRR: 1.07; 95% C.I.: 0.97-1.18; P = .192); none of the investigated covariates remained significantly independent in this model (Table 2).

Discussion

This longitudinal prospective study failed to demonstrate a significant effect of frailty severity at baseline and WMH progression at follow-up. While this relationship was noticed in unadjusted analysis, adjustment for covariates tempered this significance in a Poisson regression model. Since the included covariates did not remain significant in the fully-adjusted model, it has to be assumed that the effect of time was the main factor responsible for the above-mentioned results, with a longer exposure to frailty not being associated with WMH progression, once the effect of aging (the passage of time) is taken into account.

As previously mentioned, only a few studies have investigated whether WMH severity is related to frailty progression in the follow-up.[11,12] In one of them, both frailty and WMH severity were assessed at baseline in a small cohort of individuals aged 70 years and over. WMH severity was associated with frailty progression-as measured by the Fried's frailty phenotype-after 3 years of follow-up.[11] In another study, that used a similar basic design-but included a larger number of participants-a higher burden of WMH severity at baseline was associated with an increased frailty index after a median follow-up of 4.4 years.

Results of the above-mentioned studies are understandable as they demonstrate that baseline WMH have an impact on frailty outcomes in the follow-up. The rationale for these findings may be that WMH is associated with an abnormal gait, an increased risk of falls, recurrent strokes, and cognitive impairment, and all these manifestations may play a contributory role on frailty progression. However, the present study asks a different question, namely, is frailty at baseline independently related to WMH progression at follow-up? The answer is no. It can be argued that the process of inflammation associated with frailty is not severe enough to trigger WMH progression or that the effect of time supersedes that of frailty at baseline.

This study has limitations. The SARS-CoV-2 struck Atahualpa from April 2020, resulting in a high mortality rate among older adults.[23] In addition, several individuals left the village or declined consent for follow-up MRI

because of fears related to the pandemic. These events reduced the number of study participants with follow-up MRIs and probably contributed to a small amount of selection bias. The study population was limited to individuals of Amerindian ancestry living in a rural community. As a result, our findings may not be generalizable to other races/ethnic groups or to individuals living in large urban centers. It is also possible that some unmeasured confounders may be responsible for at least part of the findings from the present study. WMH were visually rated and this may be another limitation of this study, given that the modified Fazekas visual scale may be less reliable than volumetry for assessing slight changes in the follow-up MRI.[24] In addition, patients did not receive frailty assessment at follow-up and this could be perceived as another limitation of the present study. These limitations are counterbalanced by several strengths of this study that include its population-based cohort design (individuals were taken from the community and not from long-term care facilities), the homogeneity of the study population regarding socio-economic status and lifestyles, the systematic assessment of frailty by means of a validated field instrument, and the practice of baseline and follow-up MRIs using the same equipment and protocols.

In conclusion, this prospective cohort study failed to disclose a longitudinal association between frailty at baseline and WMH progression at follow-up. More studies are needed to corroborate our findings. These negative results open new avenues of research for a better understanding of the role of frailty in the progression of brain damage of vascular origin.

Author Contributions

OHD: study design, imaging readings, manuscript drafting; BYR: study coordinator, data collection, and analysis; DAR: data collection and analysis; RMM: statistical analysis, significant intellectual contribution to manuscript content.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORCID iDs

Oscar H. Del Brutto https://orcid.org/0000-0003-1917-8805

Denisse A. Rumbea https://orcid.org/0000-0001-8257-7572

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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