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Clinical Short Communication

Neuroimaging signatures of cerebral small vessel disease and risk of falls in stroke-free older adults living in rural Ecuador. The Atahualpa Project

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ABSTRACT

Purpose: This study aimed to assess the association between neuroimaging signatures of cerebral small vessel disease (cSVD) and the risk of falls in stroke-free older adults living in rural Ecuador.

Methods: Risk of falls was evaluated by the Downton Fall Risk Index (DFRI). MRI readings focused on white matter hyperintensities (WMH) of presumed vascular origin, deep cerebral microbleeds (CMB), silent lacunar infarcts (LI), and > 10 enlarged basal ganglia-perivascular spaces (BG-PVS). Logistic regression models were fitted to evaluate whether these neuroimaging signatures were associated with the DFRI, after adjusting for relevant confounders.

Results: We included 288 participants. The DFRI was positive in 69 (24%). Moderate-to-severe WMH were noticed in 55 individuals (19%), deep CMB in 18 (6%), LI in 23 (8%), and > 10 BG-PVS in 65 (23%). Multivariate models showed a significant association between moderate-to-severe WMH and the DFRI ($p = .016$). There were no associations between other neuroimaging signatures of cSVD and the DFRI. Age was the single covariable remaining significant in all models.

Conclusions: WMH is associated with the DFRI in stroke-free older adults living in a remote rural setting. A target for fall prevention should include the control of factors favoring the development of diffuse subcortical damage of vascular origin.

1. Introduction

Accidental falls are a major cause of morbidity and mortality among older adults living in the US, where medical costs for non-fatal fall-related injuries in 2015 totaled $31.3 billion and $637.5 million for fatal injuries [1]. These data emphasize the importance of identifying factors that increase the risk of future falls. Among such risk factors, a few studies have addressed the relationship between selected neuroimaging signatures of cerebral small vessel disease (cSVD) and the risk of future falls [2–4]. These studies have focused on individuals with white matter hyperintensities (WMH) of presumed vascular origin, while other signatures of cSVD have been generally neglected. Moreover, these data come from industrialized nations, and there is no information of this relationship among individuals living in remote rural settings, where living conditions and risk factors are different than in urban centers. By means of data obtained from of the Atahualpa Project – an ongoing population-based cohort study designed to reduce the increasing burden of stroke and other non-communicable neurological diseases in rural Ecuador – we aimed to assess the association between all neuroimaging signatures of cSVD and the risk of future falls in stroke-free community-dwelling older adults living in Atahualpa.

2. Methods

2.1. Study population

Atahualpa is homogeneous regarding ethnicity, diet, and lifestyles. Inhabitants do not migrate, and a sizable proportion of them have never visited urban centers [5]. The study population included stroke-free Atahualpa residents aged ≥60 years who had a brain MRI and assessment of the risk of future falls. The I.R.B. of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867) approved the study.

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2.2. Neuroimaging protocol

As detailed elsewhere, all Atahualpa residents aged ≥60 years were offered a brain MRI, and those with no contraindications for MRI who signed the informed consent had the exam [6]. MRIs were performed by the use of a Philips Intera 1.5 T scanner (Philips Medical Systems, Eindhoven, the Netherlands). MRI readings focused on the presence of neuroimaging signatures of cSVD. In particular, WMH were defined as lesions appearing hyperintense on T2-weighted images that remained bright on FLAIR (without cavitation) and graded according to the modified Fazekas scale [7]. Cerebral microbleeds (CMB) were identified and rated according to the microbleed anatomical rating scale; for this study, only CMB located deep in the brain were considered [8]. Lacunar infarcts were defined as fluid-filled cavities measuring 3-15 mm located in the territory of a perforating arteriole [9]. Enlarged basal ganglia perivascular spaces (BG-PVS) were defined as small (< 3 mm) structures of CSF intensity – assessed on the T2-weighted sequence – that followed the orientation of perforating arteries, and rated as abnormal if > 10 of these lesions were present in a single slice in one side of the brain [10]. All MRIs were independently read by two raters blinded to clinical information. Kappa coefficients for interrater agreement were 0.90 for WMH, 0.76 for deep CMB, 0.90 for LI, and 0.83 for the presence of > 10 enlarged BG-PVS; discrepancies were resolved by consensus.

2.3. Falls assessment

The risk of future falls was assessed by means of the Downton Fall Risk Index (DFRI), a five-question instrument inquiring about history of previous falls, use of specific medications (tranquilizers/sedatives, non-diuretic anti-hypertensives, diuretics, anti-parkinsonians, and anti-depressants), sensory or motor deficits (visual impairment, hearing impairment, paresis), gait abnormalities (with or without aid), and confusion [11,12]. Using the DFRI, a score ≥ 3 is considered positive (high risk of future falls).

2.4. Clinical covariables investigated

Demographics, alcohol intake (dichotomized in < 50 and ≥ 50 g per day), and cardiovascular risk factors were selected as confounding variables. These were assessed through interviews and procedures previously described in the Atahualpa Project [5]. We used the American Heart Association criteria to assess smoking status, physical activity, diet, the body mass index, blood pressure, fasting glucose, and total cholesterol blood levels [13]. To exclude patients with an overt stroke, rural doctors screened all participants with the use of a validated field instrument, and then, certified neurologists confirmed the diagnosis as previously reported [14].

2.5. Statistical analyses

Data analyses are carried out by using STATA version 15 (College Station, TX, USA). In univariate analyses, continuous variables were compared by linear models and categorical variables by x^2 or Fisher exact test as appropriate. Logistic regression models, adjusted for demographics, alcohol intake and cardiovascular risk factors, were fitted to assess the independent association between each of the neuroimaging signatures of cSVD and the risk of future falls (as the dependent variable), respectively.

3. Results

Of 463 individuals aged ≥60 years enrolled in the Atahualpa Project (2012–2018), 342 were active at the time of this study (January 2019). Of these, 288 (84%) were stroke-free, and had a brain MRI and fall assessment (Fig. 1). Clinical characteristics of participants and

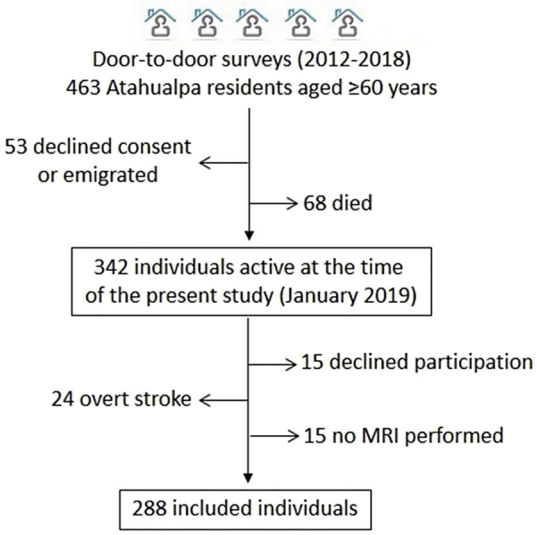

Fig. 1. Flow diagram depicting the reasons for not including potentially eligible individuals at each step of enrollment process.

across categories of the DFRI are shown in Table 1. In univariate analyses, individuals with a positive DFRI were older, more often had poor physical activity, and were more often hypertensive than those with a negative DFRI.

The DFRI was positive in 69 (24%) participants. The most common positive component of the DFRI was history of falls (151 cases, 52%), followed by use of medications (119 cases, 41%), sensory or motor deficits (117 cases, 41%), gait abnormalities (38 cases, 10%), and confusion (12 cases, 4%).

Moderate-to-severe WMH were noted in 55 individuals (19%), deep CMB in 18 (6%), LI in 23 (8%), and > 10 BG-PVS in 65 (23%). Of the investigated neuroimaging signatures, univariate logistic regression analyses showed a significant association between moderate-to-severe WMH and ≥ 10 enlarged BG-PVS, and a positive DFRI (Table 2).

A multivariate logistic regression model, adjusted for all the aforementioned confounders, showed a significant association between moderate-to-severe WMH and the DFRI (OR: 2.6; 95% C.I.: 1.2–5.7; $p = .016$); in this model, the only significant covariables were age ($p < .001$) and high fasting glucose levels ($p = .045$); high blood pressure remained marginally significant ($p = .064$). There were no independent associations between deep CMB ($p = .361$), silent LI ($p = .656$), and the presence of > 10 enlarged BG-PVS ($p = .452$) and the DFRI, in similarly fitted logistic regression models. The significant association between > 10 enlarged BG-PVS and the DFRI found in univariate analysis was suppressed in the multivariate model by the effect of confounders.

4. Discussion

Falls claim the lives of thousands of older adults every year [1]. This problem has not been investigated in remote rural settings, and little is known of the predisposing factors for falls in these populations. The present study strongly suggests that diffuse subcortical damage of vascular origin is associated with risk of future falls in our population of community-dwelling older adults. Results of the present study are consistent with studies conducted in the developed world, with the additional advantage of showing that other focal neuroimaging signatures of cSVD – deep CMB, silent LI, and > 10 enlarged BG-PVS – are not associated with an increased risk of future falls. However, these negative results should be interpreted with caution, since the small number of participants with focal neuroimaging signatures of cSVD, particularly with deep CMB and silent LI, may preclude proper assessment of these associations.

Table 1
Clinical characteristics of Atahualpa residents aged ≥60 years across categories of the Downton Fall Risk Index (univariate analyses).

	Total series (n = 288)	Risk of future falls		
		DFRI negative (n = 219)	DFRI positive (n = 69)	p value
Age, years (mean ± SD)	70.7 ± 7.9	68.6 ± 6.2	77 ± 9.2	< 0.001*
Women, n (%)	168 (58)	124 (57)	44 (64)	0.362
Heavy alcohol intake, n (%)	42 (15)	34 (16)	8 (12)	0.543
Current smokers, n (%)	11 (4)	9 (4)	2 (3)	0.920
Poor physical activity, n (%)	20 (7)	9 (4)	11 (16)	0.002*
Poor diet, n (%)	14 (5)	9 (4)	5 (7)	0.335
Body mass index ≥ 30 Kg/m^2, n (%)	66 (22)	51 (23)	15 (22)	0.920
Blood pressure ≥ 140/90 mmHg, n (%)	120 (42)	77 (35)	43 (62)	< 0.001*
Fasting glucose levels ≥ 126 mg/dL, n (%)	83 (29)	58 (26)	25 (36)	0.159
Total cholesterol ≥ 240 mg/dL, n (%)	40 (14)	32 (15)	8 (12)	0.663

DFRI: Downton Fall Risk Index.
* Statistically significant result.

Table 2
Univariate logistic regressions showing the association between the different neuroimaging signatures of cerebral small vessel disease and the risk of future falls (as the dependent variable).

Neuroimaging signature of cerebral small vessel disease	DFRI negative (n = 219)	DFRI positive (n = 69)	Odds Ratio (95% confidence interval)	p value
Moderate-to-severe white matter hyperintensities	27 (12%)	28 (41%)	4.86 (2.59–9.09)	< 0.001*
Deep cerebral microbleeds	11 (5%)	7 (10%)	2.13 (0.79–5.74)	0.133
Silent lacunar infarctions	14 (6%)	9 (13%)	2.19 (0.91–5.32)	0.082
> 10 enlarged basal ganglia perivascular spaces	37 (17%)	28 (41%)	3.36 (1.85–6.09)	< 0.001*

DFRI: Downton Fall Risk Index.
* Statistically significant result.

Diffuse subcortical brain damage of vascular origin (as evidenced on MRI by the presence of WMH) often favor the leakage of inflammatory cytokines which, in turn, disrupt the connections between the cortex and subcortical tissues. Such disruption contributes to abnormalities in balance and gait, hence increasing the risk of falls [2,3]. This effect is not seen with cSVD-related focal lesions. Of note, LI may cause gait disturbances and falls but only when located in eloquent cerebral areas (as in the case of LI-related over strokes).

Major strengths of the present study are the unbiased selection of participants and the methods used to assess neuroimaging signatures of cSVD and the risk of future falls. A potential limitation is its cross-sectional design which does not allow for an assessment of the reliability of the DFRI to predict the actual risk of falls in rural populations. Future longitudinal studies using the Atahualpa Project cohort help to answer this question. In the meantime, it seems reasonable to recommend the control of cardiovascular risk factors that favor the development of WMH in older adults living in rural settings.

5. Conclusion

Moderate-to-severe WMH, but not other focal neuroimaging signatures of cSVD, are associated with the risk of future falls in stroke-free older adults living in rural Ecuador. A target for fall prevention should include the control of factors favoring the development of diffuse subcortical damage of vascular origin.

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Conflict of interest

The authors have no financial interest related to this study.

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