Hypertensive retinopathy and cerebral small vessel disease in Amerindians living in rural Ecuador: The Atahualpa Project

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ABSTRACT

Background: Diagnosis of cerebral small vessel disease (SVD) is a challenge in remote areas where MRI is not available. Hypertensive retinopathy (HTRP) has shown to correlate with SVD in different ethnic groups, but there is no information from indigenous Latin American people. We assessed the usefulness of retinal photographs to detect cases with SVD among Amerindians living in rural Ecuador.
Methods: Atahualpa residents aged ≥ 60 years with arterial hypertension or prehypertension were identified during a door-to-door survey. A confocal line scanning laser ophthalmoscope was used to identify and grade HTRP (according to the Keith–Wagener–Barker classification). MRIs were read with attention to the presence of white matter hyperintensities (WMH) of presumed vascular origin and lacunar infarcts. Using logistic regression models, we evaluated whether HTRP was independently associated with neuroimaging signatures of SVD.
Results: Of 323 eligible candidates, 241 (75%) were enrolled. MRI readings revealed moderate-to-severe WMH in 49 (20%) cases and lacunar infarcts in 29 (12%). HTRP Grade 1 was noticed in 90 (37%) individuals and Grade 2–3 in 42 (17%). After adjusting for demographics and cardiovascular risk factors, multivariate analyses showed a significant association between Grades 2–3 HTRP and moderate-to-severe WMH (OR: 3.87, 95% C.I.: 1.64–9.13) but not with lacunar infarcts (OR: 2.22, 95% C.I.: 0.83–5.92).
Conclusion: Amerindians with HTRP Grades 2–3 are almost four times more likely to have SVD-related subcortical damage than those with no- or only Grade 1-HTRP. Retinal photographs might allow recognition of people who need further investigation and therapy.

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1. Introduction

Owing to increased life expectancy and changes in lifestyles and dietary habits, the burden of cardiovascular diseases – including stroke – is on the rise in many low- and middle-income countries [1]. Cerebral small vessel disease (SVD) – closely linked to arterial hypertension – is a major pathogenetic mechanism underlying stroke in rural areas of Latin America [2,3]. However, diagnosis of SVD requires the use of MRI, which is not readily available in these underserved populations. Efforts should be directed to find portable screening diagnostic tools that may help identify candidates for MRI screening. In this view, hypertensive retinopathy (HTRP) has been shown to correlate with imaging markers of SVD in different ethnic groups [4–7], and its recognition might be used as an inexpensive alternative to MRI to detect individuals at risk. However, there is no information on this relationship among indigenous Latin American people. In the present study, we aimed to assess the association between HTRP and neuroimaging signatures of SVD in older adults living in Atahualpa, a remote rural Ecuadorian village where previous epidemiological studies on cardiovascular risk factors have been conducted [8–10].

2. Methods

2.1. Study population

Atahualpa was selected for this study as it is representative of the region. As detailed elsewhere [11], more than 95% of the population belongs to the Native/Mestizo ethnic group (Amerindians) and their living characteristics are homogeneous. Most men belong to the blue-collar class and most women are homemakers. The diet of villagers is rich in fish and carbohydrates but poor in other types of meat and dairy products. Atahualpa is an isolated village; most residents do not migrate, and a sizable proportion of them have never visited large urban centers.

2.2. Study design

Using a population-based, cross-sectional design, Atahualpa residents aged ≥60 years were identified during a door-to-door survey and those with arterial hypertension or prehypertension – according to the JNC 7 report [12] – were eligible to participate in this study. Individuals with pre-hypertension (systolic blood pressure 120–139 mm Hg and/or diastolic blood pressure 80–89 mm Hg) were included as they are considered to have higher-than-average risk for vascular events compared to individuals with <120/80 mm Hg [12,13]. The protocol and the informed consent form were approved by the I.R.B. of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867).

2.3. Blood pressure determinations

Under comfortable room temperature levels, the arterial blood pressure was measured in both arms by trained medical students with the use of a manual sphygmomanometer (Welch Allyn Tycos© 7670-01), following a well-defined protocol [14]. In brief, with the person in the sitting position and after resting for at least 10 min, the blood pressure was measured three times (at each arm) at intervals of 2 min, and the highest mean value of the readings between right and left arms was used for analysis. Participants who admitted coffee intake or cigarette smoking before the procedure, were screened 1 h later.

2.4. Cardiovascular risk factors

Cardiovascular risk factors were evaluated by direct interviews and procedures previously used in the Atahualpa Project [8]. Smoking status and physical activity were based on self-report, and diet was assessed with the aid of a validated food frequency questionnaire. The body mass index (BMI) was calculated after obtaining the person's height and weight. Fasting glucose and total cholesterol levels were measured after obtaining a capillary blood sample, using Accu-chek® Active and Accutrend® Plus devices (Roche Diagnostics, Mannheim, Germany), respectively.

2.5. Retinal photographs

The Easy Scan v1.2 (i-Optics B.V., The Hague, The Netherlands) was used for taking retinal photographs. This zero-dilatation smart retinal imaging system uses confocal line scanning laser ophthalmoscope technology to illuminate the retina through a 2 mm pupil, and can better penetrate media opacities than conventional fundus cameras [15]. All exams were performed at the Community Center of the Atahualpa Project by trained medical students. A certified ophthalmologist reviewed all images, blinded to clinical data and MRI findings. HTRP grading was determined according to the Keith–Wagener–Barker classification [16], which includes: Grade 1, mild generalized retinal arteriolar narrowing; Grade 2, definite focal narrowing and arteriovenous nicking; Grade 3, signs of Grade 2 retinopathy plus retinal hemorrhage, exudate, and cotton-wool spots; and Grade 4, signs of Grade 3 retinopathy plus papilledema. When HTRP Grades of the two eyes differed, the more advanced grade was recorded for that individual.

2.6. Neuroimaging protocol

We used data from brain MRIs performed in the year prior the current survey to get information on the presence of neuroimaging signatures of SVD. All studies had been performed for the Atahualpa Project at Hospital Clínica Kennedy (Guayaquil) with the use of a Philips Intera 1.5T machine (Philips Medical Systems, the Netherlands), following a standardized protocol described elsewhere [3]. Lesions of interest included white matter hyperintensities (WMH) of presumed vascular origin and lacunar infarcts. 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 [17], and lacunar infarcts were defined as fluid-filled cavities measuring 3–15 mm located in the territory of a perforating arteriole [18]. As previously detailed, two experienced readers independently reviewed all MRIs, blinded to clinical manifestations and cardiovascular risk factors. Inter-rater agreement was assessed for all findings, and disagreements were resolved by consensus. Kappa coefficients for inter-rater agreements were 0.91 (95% C.I.: 0.86–0.95) for WMH, and 0.90 (95% C.I.: 0.82–0.98) for lacunar infarcts.

2.7. Statistical analyses

Data analyses are carried out by using STATA version 14 (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. Using multivariate logistic regression models, we evaluated whether HTRP is independently associated with WMH of presumed vascular origin and with lacunar infarcts (as the dependent variables), after adjusting for demographics and cardiovascular risk factors.

3. Results

The door-to-door survey identified 323 eligible candidates, 241 (75%) of whom were included. The remaining individuals either declined to sign the informed consent or did not have a brain MRI. Mean age of participants was 71 ± 7 years, 142 (59%) were women, seven (3%) were current smokers, 49 (20%) had a body mass index ≥30 kg/m², 16 (7%) had poor physical activity, 10 (4%) had a poor diet, 79 (33%) had fasting glucose levels ≥126 mg/dL, and 32 (13%) had total cholesterol blood levels ≥240 mg/dL. Blood pressure levels were ≥140/90 in 161 (67%) individuals and between 120 and 139/80–89 mm Hg in the remaining 80. Changes compatible with HTRP were noticed in 132 (55%) cases, most of whom (90 out of 132, 68%) were classified as Grade 1. Of the remaining 42 cases, 39 had Grade 2 and three had Grade 3 HTRP (eight of these individuals also had evidence of diabetic retinopathy). MRI readings revealed moderate-to-severe WMH in 49 (20%) cases and lacunar infarcts in 29 (12%). Lacunar infarcts were single in all but two cases, and were located in the subcortical white matter of cerebral hemispheres in 14 cases, in the basal ganglia/thalamus in 11, and in the brainstem/cerebellum in the remaining four.

Univariate analyses with individuals classified according to whether they had any Grade of HTRP or not, showed no differences in demographics, cardiovascular risk factors or in neuroimaging signatures of SVD across both groups. In contrast, when individuals with Grades 2–3 HTRP (n = 42) were compared to those with no- and Grade 1-HTRP (n = 199), moderate-to-severe WMH were significantly more common in the former ($p = 0.012$), but the prevalence of lacunar infarcts was similar across groups (Table 1). Multivariate logistic regression models also showed a significant association between Grades 2–3 HTRP and the presence of moderate-to-severe WMH (OR: 3.87, 95% C.I.: 1.64–9.13, $p = 0.002$) but not with lacunar infarcts (OR: 2.22, 95% C.I.: 0.83–5.92, $p = 0.111$), after adjusting for relevant confounders.

4. Discussion

This population-based study, conducted in pre-hypertensive and hypertensive older Amerindians living in rural Ecuador, shows a significant association between HTRP and WMH but not with lacunar infarcts. However, this association was confined to individuals having HTRP Grades 2–3, suggesting that the severity of microvascular damage plays a role in this relationship (Fig. 1). Our findings are in line with the Age, Gene/Environment Susceptibility—Reykjavik Study, which showed that focal narrowing of retinal arteries and arteriovenous nicking (characteristics of Grade 2 HTRP) are associated with vascular damage of the