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# Intracranial arterial stenosis in Ecuadorian Natives/Mestizos. A population-based study in older adults (The Atahualpa Project)

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ABSTRACT

*Background:* Intracranial arterial stenosis (IAS) is more prevalent among Asians, Blacks and Caribbean Hispanics than in Whites. However, there is no information on the importance of this common cause of stroke among Mestizo/Native populations of Latin America. We aimed to assess prevalence and correlates of IAS in an indigenous Ecuadorian population of older adults.
*Methods:* Atahualpa residents aged ≥60 years were identified during door-to-door surveys and invited to undergo brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of intracranial vessels for identification of stroke lesions and arterial stenosis. Prevalence of IAS was assessed in patients with strokes as well as in stroke-free individuals. A logistic regression model was constructed with stroke as the outcome, IAS as the exposure, and confounders (demographics and cardiovascular risk factors) as independent variables.
*Results:* Out of 267 participants (mean age 71 ± 8 years, 57% women), 15 (5.6%) had intracranial arterial stenosis, including 10 out of 52 (19.2%) persons with stroke and five out of 215 (2.3%) without. The multivariate logistic regression model showed significant association of IAS with stroke after adjusting for demographics and cardiovascular risk factors (OR: 7.9, 95% C.I.: 2.2–27.8, $p = 0.001$). Mechanisms underlying stroke in patients with IAS included perforator occlusion, artery-to-artery embolism and hypoperfusion.
*Conclusions:* Prevalence of IAS in Ecuadorian Natives/Mestizos is similar to that in Asians. Individuals aged ≥60 years with IAS are almost eight times more likely to have a stroke after adjusting for confounding variables.



## 1. Introduction

Intracranial arterial stenosis (IAS) – mostly related to atherosclerosis – is a common cause of stroke in older adults (Battistella & Elkind, 2014). While several studies have shown differences in the prevalence of IAS according to race/ethnicity, most of them have been conducted in stroke patients, and little is known on the importance of IAS in the population at large (Suri & Johnston, 2009). In the Northern Manhattan Study, IAS was 5–6 times more prevalent among Blacks and Caribbean Hispanics than in Whites (White et al., 2005). In rural China, prevalence of IAS was 6.9% among adult dwellers (Wong et al., 2007) and that of stenosis of the middle cerebral artery was 5.9% (Huang et al., 2007); both studies used transcranial Doppler for diagnosis. A recent study in stroke-free Spaniards older than 50 years revealed a 3.3% prevalence of moderate-to-severe IAS (López-Cancio et al., 2012). There is a need for information on the burden of IAS among Mestizo/Native populations of Latin America, particularly because stroke prevalence is steadily increasing in the region, and the implementation of preventive strategies must be based on local studies evaluating region-specific risk factors. We aimed to assess prevalence and correlates of IAS by the use of magnetic resonance angiography (MRA) in a population of older Natives/Mestizos enrolled in the Atahualpa Project, an ongoing population-based cohort study designed to reduce the burden of stroke in rural Ecuador (Del Brutto, 2013).

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## 2. Methods

### 2.1. Population studied

Atahualpa is a closed village located in rural coastal Ecuador. Historical evidence suggest that the village already existed by the time Spaniards arrived to Ecuador, and the current population has little evidence of cross breading. More than 95% of the population belongs to the Native/Mestizo ethnic group. Phenotypically, Atahualpa's residents have an olive-moderate brown skin, dark brown eyes and hair, and are of short stature. We recently demonstrated a high prevalence (79%) of a Friedman's palate position type IV in these individuals, which is probably genetically determined since Amerindians have a predominantly elliptic hard palate (Castillo, Mera, Zambrano, & Del Brutto, 2014).

### 2.2. Study design

All Atahualpa residents aged ≥60 years identified during yearly door-to-door surveys and prospectively registered in the Atahualpa Project from 2012 to 2015 have been offered a brain magnetic resonance imaging (MRI) and MRA of intracranial vessels. Out of 374 participants, 267 (71%) were enrolled in this imaging sub-study. Reasons for not performing neuroimaging included refusal to sign the informed consent, severe disability, contraindications for MRI and claustrophobia. There were no significant differences in the mean age or in the percentage of women across participants and non-participants. The Institutional Review Board of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867) approved the protocol and the informed consent.

### 2.3. Neuroimaging protocol

Exams were performed with a Philips Intera 1.5T (Philips Medical Systems, the Netherlands) at Hospital-Clínica Kennedy, Guayaquil. MRI included two-dimensional multi-slice turbo spin echo T1-weighted, fluid attenuated inversion recovery (FLAIR), T2-weighted, and gradient-echo sequences in the axial plane, as well as a FLAIR sequence oriented in the sagittal plane; slice thickness was 5 mm with 1 mm gap between slices. MRA was performed using a three-dimensional time-of-flight sequence; slice thickness was interpolated down at 1 mm (Del Brutto, Mera, Del Brutto, Zambrano, & Lama, 2015; Del Brutto, Mera, Zambrano, & Lama, 2015). A neuroradiologist (JL) and a neurologist (OHD) independently read all imaging studies, blinded to clinical data. MRIs were reviewed to assess the presence of cerebrovascular lesions. On MRA, primary interest focused on the presence of significant (>50%) segmental stenosis of major intracranial arteries. Kappa coefficients for inter-rater agreement were 0.74 (95% C.I.: 0.58–0.90) for the presence of IAS, and disagreements were resolved by consensus.

### 2.4. Assessment of cardiovascular risk factors and overt stroke

Demographics and cardiovascular risk factors were evaluated by interviews with validated questionnaires. Smoking status and physical activity were based on self-report, and diet was assessed with the aid of a food frequency questionnaire. The body mass index 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. BP was measured following a well-defined protocol (Del Brutto, Peñaherrera, Ochoa, Santamaría, Zambrano, & Del Brutto, 2014). To recognize patients with overt strokes, rural doctors screened all persons with the use of a validated field instrument, and then, certified neurologists confirmed the diagnosis.

### 2.5. Statistical analyses

All analyses are carried out by using STATA version 13 (College Station, TX, USA). Descriptive statistics are presented as means ± standard deviations for continuous variables and as percentages with 95% C.I. for categorical variables. Prevalence of IAS was assessed in patients with strokes as well as in stroke-free individuals. A logistic regression model was constructed with stroke as the outcome, IAS as the exposure, and confounders (demographics and cardiovascular risk factors) as independent variables.

## 3. Results

Mean age of the 267 participants was 71 ± 8 years and 152 (57%) were women. MRI showed strokes in 52 (19.5%) individuals. Of them, 43 had one or more lacunar infarcts – defined as fluid-filled cavities measuring 3–15 mm – located in the subcortical white matter, basal ganglia or brainstem; seven had cortical infarcts located in the territory of the middle or posterior cerebral arteries; and five had old parenchymal brain hemorrhages. Some patients had more than one type of cerebrovascular lesions. Collating clinical and MRI data, silent strokes were found in 28 out of these 52 persons (all lacunar infarcts).

Fifteen out of 267 participants (5.6%) had IAS, including 10 out of 52 (19.2%) persons with stroke and five out of 215 (2.3%) without. Persons with IAS were older than those with normal arteries but, with the exception of a poorer physical activity, there were no differences in cardiovascular risk factors across groups (Table 1). The multivariate logistic regression model showed significant association of IAS with stroke after adjusting for demographics and cardiovascular risk factors (OR: 7.9, 95% C.I.: 2.2–27.8, $p = 0.001$).

IAS were considered symptomatic in seven out of 15 cases (47%). In such cases, either a cortical ($n = 4$) or a lacunar ($n = 3$) infarct were located in the vascular territory supplied by the affected artery. In the eight remaining cases – including five

**Table 1**
Cardiovascular risk factors[a] according to the presence of intracranial arterial stenosis (univariate analysis).

| | Total series ($n = 267$) | Intracranial arterial stenosis ($n = 15$) | Normal MRA ($n = 252$) | Significance ($p$ value) |
|---|---|---|---|---|
| Age, years (mean ± SD) | 71 ± 8 | 75 ± 11 | 71 ± 8 | 0.049 |
| Women, $n$ (%) | 152 (57%) | 6 (40%) | 146 (58%) | 0.173 |
| Current smoker, $n$ (%) | 4 (1.5%) | 0 | 4 (1.6%) | 0.623 |
| BMI ≥ 30 kg/m$^2$, $n$ (%) | 54 (20%) | 3 (20%) | 51 (20%) | 0.982 |
| Poor physical activity, $n$ (%) | 27 (10%) | 4 (27%) | 23 (9%) | 0.03 |
| Poor diet, $n$ (%) | 8 (3%) | 0 | 8 (3%) | 0.488 |
| Total cholesterol ≥ 240 mg/dL, $n$ (%) | 30 (11%) | 2 (13%) | 28 (11%) | 0.791 |
| Blood pressure ≥ 140/90 mmHg, $n$ (%) | 133 (50%) | 10 (67%) | 123 (49%) | 0.179 |
| Fasting glucose ≥ 126 mg/dL, $n$ (%) | 90 (34%) | 5 (33%) | 85 (34%) | 0.974 |

[a] Cardiovascular risk factors assessed at the time of enrollment and MRA practice. Subsequent determinations of blood pressure, fasting glucose, and cholesterol blood levels were not considered in this study.