Incompleteness of the Circle of Willis Correlates Poorly with Imaging Evidence of Small Vessel Disease. A Population-based Study in Rural Ecuador (the Atahualpa Project)

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Background: Studies looking for an association between incompleteness of the Circle of Willis (CoW) and small vessel disease (SVD) markers are scarce and conflicting. We aimed to evaluate this association in an unbiased population-based study conducted in Atahualpa (rural Ecuador). *Methods:* Atahualpa residents 60 years of age or more were identified during a door-to-door survey and invited to undergo magnetic resonance imaging for identification of SVD markers, including white matter hyperintensities (WMHs), strokes, and deep microbleeds. Magnetic resonance imaging (MRA) was used for classifying the CoW according to the presence or absence of one A_1 segment of the anterior cerebral artery or one or both P_1 segments of posterior cerebral arteries. *Results:* Of 311 eligible persons, 258 were enrolled. Mean age was 70 ± 8 years, 59% were women, and 74% had a poor cardiovascular health (CVH) status. Of these, 172 patients (67%) had WMH, 40 patients (16%) had SVD-related strokes, and 23 patients (9%) had deep microbleeds. MRA revealed a complete CoW in 157 persons (61%). Persons with SVD markers were older than those without markers ($P < .0001$). A poor CVH status was noted in 79% of persons with at least 1 SVD marker and in 65% of those with no markers ($P = .02$). Logistic regression models showed no association of incompleteness of the CoW with any marker of SVD—alone or in combination—after adjusting for age, sex, and CVH status. *Conclusions:* Lack of association between incompleteness of CoW and SVD markers suggest that genetically determined variants in the intracranial vasculature are not responsible for the high prevalence of SVD among native South American populations. **Key Words:** Circle of Willis—cerebral small vessel disease—white matter hyperintensities—cerebral microbleeds—lacunar strokes—Atahualpa Project.

Introduction

An association between incompleteness of the circle of Willis (CoW) and the presence of markers of cerebral small vessel disease (SVD) has been suggested based on the premise that insufficient collateral blow flow increases the vulnerability of the subcortical white matter to hypotension-induced low flow effects.[1] In some hospital-based registries, the prevalence of lacunar strokes[2] or white matter hyperintensities (WMHs) of presumed vascular origin[3] were found to be increased in persons with an incomplete CoW compared with those with a full CoW configuration. However, this information is not conclusive to date.[4-6]

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In the event that incompleteness of the CoW associates with markers of SVD, these anatomic variants have to be seen as nonmodifiable risk factors that should be recognized before adverse vascular outcomes (overt strokes and cognitive decline) occur. Relevance of nonmodifiable risk factors must be assessed in specific ethnic groups and populations to settle their actual role on the burden of stroke at regional levels. In the present study, we aimed to assess the association between incompleteness of the CoW and markers of SVD in community-dwelling elders identified during a door-to-door survey in rural Ecuador.

Methods

We extended an invitation to undergo magnetic resonance imaging (MRI) of the brain and magnetic resonance angiography (MRA) of intracranial vessels to all participants of the Atahualpa Project 60 years of age or more. As detailed elsewhere, this is an ongoing population-based cohort study designed to reduce the increasing burden of stroke and other noncommunicable diseases in rural Ecuador.[7,8] The protocol and the informed consent form were approved by the institutional review board of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867).

The cardiovascular health (CVH) status of all enrolled individuals was assessed by the use of the 7 metrics proposed by the American Heart Association, including smoking status, body mass index, physical activity, diet, blood pressure, fasting glucose, and total cholesterol blood levels.[9] Each metric was categorized as ideal, intermediate, and poor, and the CVH status was classified as poor if at least 1 metric was in the poor range. To recognize persons with an overt stroke, rural doctors screened all persons with the use of a validated field questionnaire, and then, certified neurologists confirmed the diagnosis as previously described.[10]

Imaging studies were performed with a Philips Intera 1.5 T (Philips Medical Systems, Eindhoven, the Netherlands) at Hospital-Clínica Kennedy, Guayaquil. MRI included 2-dimensional multislice 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 3-dimensional time-of-flight sequence; slice thickness was interpolated down at 1 mm. We used the pre-established brain imaging package delivered by the manufacturer to homogenize applicability by technicians.

MRIs and MRAs were independently reviewed by 2 experienced readers (O.H.D. and J.L.), blinded to clinical manifestations and CVH status. Inter-rater agreements were assessed for all findings, and disagreements were resolved by consensus. On MRI, interest was focused on the presence of markers of SVD, including WMH of presumed vascular origin, SVD-related strokes (lacunar infarctions and deep parenchymal brain hemorrhages), and deep cerebral microbleeds (Fig 1). 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.[11] Lacunar infarcts were defined as fluid-filled cavities measuring 3-15 mm located in the territory of a perforating arteriole,[12] and cerebral microbleeds were identified and rated according to the Microbleed Anatomical Rating Scale.[13]

According to Horikoshi et al,[14] a complete CoW was named "O" (ordinary type), and incomplete CoW was named "A" (anterior type, in which one A_1 segment of the anterior cerebral artery is not visualized) and "P" (posterior type, in which one P_1 segment of the posterior cerebral artery is not visualized, and P_2 and P_3 segments were delineated continuously with the ipsilateral posterior communicating artery). Combinations of these variants of incomplete CoW included the anterior-posterior, posterior-posterior, and anterior-posterior-posterior types (Fig 2).

Descriptive statistics were presented as means with standard deviations for continuous variables and as percentages for categorical variables. Kappa statistics were

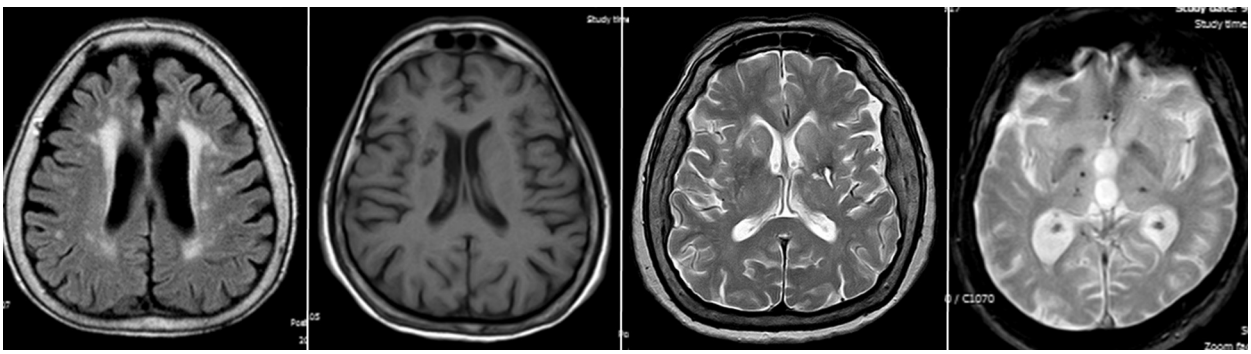

Figure 1. *Magnetic resonance imaging markers of cerebral small vessel disease. From left to right: white matter hyperintensities of presumed vascular origin (fluid-attenuated inversion recovery–TR 9000, TE 120, TI 2500), lacunar infarct in subcortical white matter (T1-weighted–TR 594, TE 15), putaminal hemorrhage (T2-weighted–TR 4500, TE 100), and deep microbleeds (gradient-echo–TR 686, TE 23). Abbreviations: TR, repetition time; TE, echo time.*