

## Calcified Neurocysticercosis Associates with Hippocampal Atrophy: A Population-Based Study

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**Abstract.** Calcified neurocysticercosis has been associated with hippocampal atrophy in patients with refractory epilepsy, but the relevance of this association in the population at large is unknown. We assessed calcified cysticerci and its association with hippocampal atrophy in elderly persons living in Atahualpa, an Ecuadorian village endemic for neurocysticercosis. All Atahualpa residents  $\geq 60$  years of age were invited to undergo computed tomography/magnetic resonance imaging for neurocysticercosis detection. Twenty-eight (11%) out of 248 enrolled persons had calcified cysticerci (case-patients) and were matched 1:1 by age, sex, and years of education to individuals without neurocysticercosis on computed tomography/magnetic resonance imaging (controls). Four case-patients and none of the controls had epilepsy ( $P = 0.134$ ). Cognitive performance was similar across both groups. The Scheltens' medial temporal atrophy scale was used for hippocampal rating in case-patients and matched controls without neurocysticercosis. Mean score in the Scheltens' scale was higher in case-patients than in controls ( $P < 0.001$ ). Atrophic hippocampi were noticed in 19 case-patients and five controls ( $P = 0.003$ ). Atrophy was bilateral in 11 case-patients and unilateral in eight. All case-patients with unilateral hippocampal atrophy had at least one ipsilateral calcification. This study shows an association between calcified cysticerci and hippocampal atrophy and raises the possibility of an inflammation-mediated hippocampal damage as the responsible mechanism for these findings.

### INTRODUCTION

Although parenchymal brain calcified cysticerci have traditionally been considered inert lesions with little clinical relevance, its contribution to the burden of neurological disease may be significant. In endemic regions, the numbers of patients with only calcified neurocysticercosis (NCC) and active epilepsy are quite large. Moreover, parenchymal calcifications can be associated with focal edema by the time of a seizure or a headache episode, likely reflecting periodical exposure of trapped antigens to the host's immune system and subsequent inflammation.<sup>1–4</sup> An association between calcified NCC and hippocampal atrophy has also been suggested based on studies of patients with refractory epilepsy, but the actual prevalence and relevance of this association is largely unknown.<sup>5–8</sup> Here, we report the results of a population-based and a nested case-control study aimed to assess the prevalence of calcified cysticerci and its association with hippocampal atrophy in community-dwelling elderly persons living in Atahualpa, a rural Ecuadorian village where NCC is endemic.<sup>9</sup> The study focused on individuals  $\geq 60$  years of age to cover the possibility that such association exists but take a long time to develop.

### METHODS

The study was conducted in Atahualpa, a coastal rural community in Ecuador where previous epidemiological studies on NCC have been performed.<sup>9,10</sup> All residents  $\geq 60$  years of age were invited to undergo non-enhanced brain computed tomography (CT) and magnetic resonance

imaging (MRI). The institutional review board (IRB) of the Hospital-Clinica Kennedy in Guayaquil, Ecuador (FWA 00006867) approved the protocol and the informed consent.

Exams were performed with a Philips Brilliance 64 CT scanner and a Philips Intera 1.5T MRI machine (Philips Medical Systems, Eindhoven, The Netherlands) at Hospital-Clinica Kennedy, Guayaquil. The CTs were obtained in the axial plane with sagittal and coronal reconstructions; slice thickness was 3 mm with no gap between slices. The 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, and a T1-weighted sequence oriented in the sagittal plane. We used the pre-established brain imaging package delivered by the manufacturer to assure uniformity of the data. Slice thickness was 5 mm with 1 mm gap between slices.

A neurologist (OHD) and a neuroradiologist (JL) independently read all CTs and MRIs with attention to the presence of parenchymal brain calcifications and other abnormalities suggestive of NCC. Images corresponding to all identified lesions were sent to another expert (HHG) for further confirmation. As previously described, rounded and homogeneous non-physiological supratentorial calcifications, measuring  $< 1$  cm in diameter and not explained by any other cause, were considered of cysticercotic origin.<sup>11,12</sup> Inter-reader agreement was excellent ( $k = 0.92$ ) and disagreements were resolved by consensus.

Persons with calcified cysticerci (case-patients) were matched 1:1 by age, sex, and years of education to individuals with no calcifications or any other evidence of NCC on CT/MRI (controls). Case-patients and controls were interviewed by one of the authors (VJD), blinded to neuroimaging findings. History taking was directed to find evidence of a seizure disorder with emphasis of age of onset and date of the last seizure, number of lifetime seizures, type of seizures, and antiepileptic drug use and efficacy;

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a complete neurological examination was performed and any abnormality was noticed. Cognitive performance was assessed by the use of the Spanish version of the Montreal Cognitive Assessment (MoCA) test ([www.mocatest.org](http://www.mocatest.org), Z. Nasreddine MD, version 07 November 2004) and the Leganés Cognitive Test (Prueba Cognitiva de Leganés). The MoCA evaluates major cognitive domains, including visuospatial-executive, language, short-term memory, abstraction, attention, calculation, and orientation, for a maximum score of 30 points.<sup>13</sup> The Leganés Cognitive Test mainly evaluates orientation and memory. It is a reliable instrument (originally developed in Spanish) used in elderly persons living in poor-educated communities; the maximum score is 32 points, and a score of  $\leq 22$  indicates dementia.<sup>14</sup>

Case-patients and controls had an additional T1-weighted inversion recovery sequence (acquisition time 3:31 min, repetition time 2.250 msec, echo time 11 msec, and inversion time 400 msec) for hippocampal evaluation, which was oriented in the coronal plane and perpendicular to the long axis of the temporal bone; slice thickness were 4 mm with no gap between slices. These images were sent to an independent expert neuroradiologist (PS) and a neurologist (XC) blinded to other imaging findings and to case/control status. Hippocampi were rated using the Scheltens' medial temporal atrophy scale,<sup>15</sup> which grades the width of the choroid fissure, the width of the temporal horn, and the height of the hippocampus on a five-point visual rating scale ranging from 0 (no atrophy) to 4 (severe atrophy). Up to 1 point for persons  $< 75$  years of age, and 2 points for persons  $\geq 75$  years of age were considered age-related changes. Each temporal lobe was rated separately, and any asymmetry  $\geq 1$  point was noted.

Descriptive statistics were presented as means with standard deviations for continuous variables and as percentages with 95% confidence interval (CI) for categorical variables. Statistical significance was tested by the use of the McNemar's test for correlated proportions (matched-pair analysis). Values of  $P < 0.05$  were considered significant.

## RESULTS

Out of 2,478 Atahualpa residents identified during a door-to-door survey, 311 were  $\geq 60$  years of age. Of these, 258 (83%) underwent both CT and MRI. Reasons for not performing neuroimaging included refusal to participate ( $N = 26$ ), severe disability ( $N = 11$ ), claustrophobia ( $N = 8$ ), and implanted pacemaker ( $N = 1$ ); six additional persons had died and one emigrated between the survey (October 2013) and the invitation (February 2014). Motions and metal artifacts (mostly dentures) precluded proper imaging reading in 10 of the 258 scanned persons and were not considered for analyses. Figure 1 is a flow diagram depicting the process of enrollment and the reasons for not including potentially eligible individuals.

Mean  $\pm$  SD age of the 248 participants was  $70 \pm 8$  years, 146 (59%) were women, and 206 (83%) had only primary school education. Calcified cysticerci were found in CT in 28 individuals (11%, 95% CI: 8–16%). There was a single cerebral calcification in 22 cases, two in five cases, and the remaining patient had seven calcifications. Associated colloidal cysts were noticed in one person with a single calcification and in another with seven calcifications. The

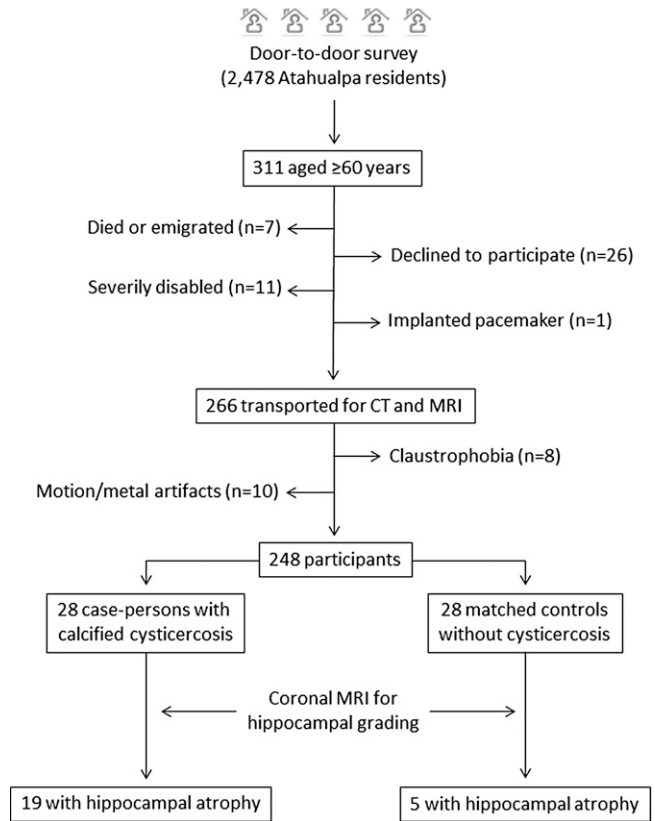


FIGURE 1. Flow diagram showing the process of enrollment and the number of participants in this study.

MRI detected the calcifications shown on CT in only 18 of 28 cases (65%), mostly on T2-weighted and gradient-echo sequences; the two colloidal cysts were evident on all MRI sequences and were also visible on CT.

As expected, case-patients and their 28 matched controls were similar in regards to the matched variables, including age ( $69 \pm 6$  years), sex (71% women), and education level ( $7 \pm 3$  years). Clinical interview revealed a chronic seizure disorder in four case-patients and in none of the controls ( $P = 0.134$ ). Seizures were recurrent in all cases and started at ages ranging from 12 to 62 years. All these patients had  $> 20$  lifetime seizures and three of them still had active epilepsy, which was poorly controlled by medication in two. Seizures were tonic-clonic generalized in three (one with complex partial seizures) and simple partial in one; no patient had history of status epilepticus. Mean scores in the MoCA test were  $19.1 \pm 4.7$  for case-patients and  $18.4 \pm 4.8$  for controls ( $P = 0.584$ ). According to the Leganés Cognitive Test, only two case-patients and none of the controls had scores below the recommended cut-off level for dementia, with mean  $\pm$  SD scores of  $27.4 \pm 2.7$  for case-patients and  $27.3 \pm 1.8$  for controls ( $P = 0.871$ ).

Kappa coefficients for inter-rater agreements of findings in the T1-weighted inversion recovery MRI sequence were 0.61 for unilateral, 0.82 for bilateral, and 0.85 for any kind of hippocampal atrophy. After consensus, mean  $\pm$  SD points in the Scheltens' scale for all rated hippocampi ( $N = 112$ , two per person, in 28 case-patients and 28 controls) were  $3.9 \pm 1.5$  for case-patients and  $2.8 \pm 1.2$  for controls ( $P < 0.001$ ). A total of 19 (68%, 95% CI: 49–82%)

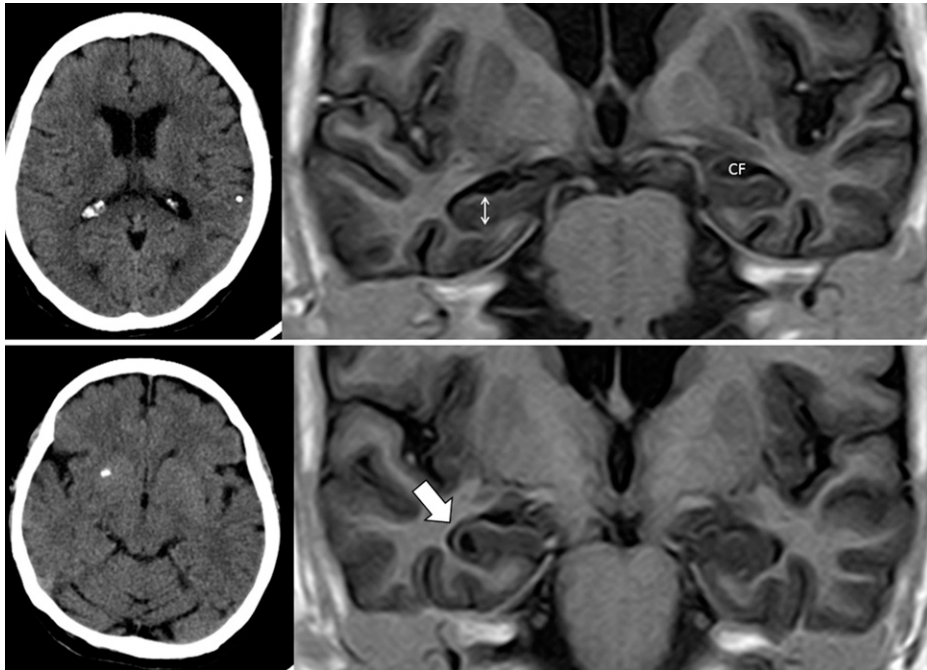


FIGURE 2. **Upper panel:** Plain computed tomography (CT) (left) showing single calcified cysticercus in left parietal lobe and T1-weighted inversion recovery magnetic resonance imaging (MRI) sequence (right) showing bilateral hippocampal atrophy (Grade 3 in the Scheltens' medial temporal atrophy scale), characterized by increased width of the choroid fissure (CF) and decreased height of hippocampal formation (double-headed arrow). **Lower panel:** Plain CT (left) showing single calcified cysticercus in right basal ganglia and T1-weighted inversion recovery MRI sequence (right) showing ipsilateral hippocampal atrophy (thick arrow).

case-patients and five (18%) controls had hippocampal atrophy (odds ratio [OR]: 5.7, 95% CI: 1.7–19.3,  $P = 0.003$ ), which was bilateral in 11 case-patients and four controls, and unilateral in eight case-patients and in only one control (Figure 2). Bilateral hippocampal atrophy was not more prevalent among case-patients with a single calcification than in those with more than one calcifications. In all the eight case-patients with unilateral hippocampal atrophy there was at least one calcification in the affected side. There were no age- and sex-related differences between case-patients with normal hippocampi and those with uni- or bilateral hippocampal atrophy. Epilepsy was present in three case-patients with bilateral hippocampal atrophy and in one with normal hippocampus.

## DISCUSSION

This study shows a rather high prevalence of calcified cysticerci in elderly persons living in Atahualpa, a finding that has also been shown in other cysticercotic-endemic villages of South America.<sup>16</sup> Of importance, a significantly higher prevalence of hippocampal atrophy (bilateral and unilateral) is noted among our participants with calcified NCC when compared with controls.

Much remains to be learned on the relationship between calcified NCC and hippocampal atrophy. Current evidence shows that these conditions often co-exist in cysticercotic-endemic areas, but to what extent this occurs just by chance remains to be determined, because this association has not been investigated in the population at large. Information derived from a series of patients with medial temporal lobe epilepsy strongly suggest a cause-and-effect relationship between calcified NCC and hippocampal atrophy, on the basis

of differences in the characteristics and severity of seizures among patients with both conditions when compared with those with hippocampal atrophy alone.<sup>5–7</sup> In this context, it has been suggested that calcified cysticerci lead to hippocampal atrophy by causing recurrent seizures or status epilepticus, and the resulting hippocampal atrophy—in turn—exacerbates the seizure disorder. Parasites may not be necessarily located within limbic circuits, suggesting a remote deleterious effect of seizures on hippocampal neurons.<sup>17–19</sup>

An alternative hypothesis proposes that, irrespective of the occurrence of seizures, calcified cysticerci might lead to variable inflammatory responses and inflammation-mediated hippocampal damage associated or not with a genetic predisposition.<sup>20,21</sup> In this view, periodic remodeling of calcified cysticerci with exposure of trapped parasitic antigens to the host's immune system,<sup>3,4,22</sup> might account for episodic inflammatory events, and seizures may not be a necessary trigger for hippocampal atrophy. Although this has not been shown in humans, experimental evidence showing that repeated endotoxin exposure and increased levels of pro-inflammatory cytokines correlate with hippocampal damage, support the hypothesis of inflammatory-mediated atrophy.<sup>23</sup> In our study population only a minority of persons (3 out of 19) with both calcified NCC and hippocampal atrophy had a history of seizures, and this supports the inflammatory hypothesis. We cannot, however, rule out subclinical epileptiform activity in our patients because electroencephalogram (EEG) recordings were not obtained.

Selective hippocampal atrophy has been recognized as a marker of Alzheimer's disease and other forms of degenerative dementias on neuroimaging studies,<sup>24</sup> and it could be argued that more persons with these disorders were inadvertently included among our case-patients. However,

similar cognitive performances across case-patients and controls in this study discard this possibility. Both the MoCA and the Leganés Cognitive Test appear to be simple and reliable options to assess different cognitive domains and have previously been used and validated to evaluate cognition in Latin American underserved populations, including Atahualpa.<sup>25,26</sup> Our results also support previous findings showing that cognition is not particularly impaired in NCC patients with hippocampal atrophy.<sup>27</sup>

Major strengths of our study include the population-based design, the unbiased characteristics of scanned persons, the method used for choosing controls, the blinded imaging rating, and the expertise (> 20 years) of involved readers. Although the lack of hippocampal volume measurements is a potential weakness of our study, the Scheltens' medial temporal atrophy scale has proved reliable for visual grading hippocampal atrophy when compared with volumetric assessment.<sup>28</sup> Immune tests were not performed because results of either antibody or antigen detection may be erratic in patients only presenting with calcified cysticerci, leading to diagnostic misinterpretations.<sup>29</sup>

In summary, this study shows a significant association between calcified NCC and hippocampal atrophy in people  $\geq 60$  years of age living in an endemic community. People living in rural-endemic areas most often acquire cysticercosis during adolescence or early adulthood, therefore we are most likely dealing with chronic, old infections that were present long before hippocampal atrophy. However, a case-control study is not proof for causality. Subsequent cohort studies should scan younger populations to evaluate whether calcified cysticerci are related to the development of hippocampal atrophy in the long-term follow-up and to whether such atrophy correlates with the occurrence of temporal lobe epilepsy.

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