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The Association between Calcified Neurocysticercosis and Cognitive Performance: A Case–Control Study Nested to a Population-Based Cohort

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Abstract. Mechanisms implicated in the association between neurocysticercosis (NCC) and cognitive impairment remain unknown. Atahualpa residents aged ≥ 40 years with calcified NCC were identified as case patients and paired 1:1 to age- and gender-matched controls. The selection process generated 79 pairs. Cognitive performance was measured by the Montreal Cognitive Assessment (MoCA). A conditional logistic regression model revealed no differences in MoCA scores across case patients and controls, after adjusting for education, epilepsy, depression, and hippocampal atrophy. The single covariate remaining significant was hippocampal atrophy. When participants were stratified according to this covariate, linear models showed lower MoCA scores among case patients (but not controls) with hippocampal atrophy. In a fully adjusted linear regression model, age remained as the single covariate explaining cognitive impairment among NCC patients. This study demonstrates an association between hippocampal atrophy and poor cognitive performance among patients with calcified NCC, most likely attributable to the effect of age.

Poor cognitive performance is often mentioned as a manifestation of neurocysticercosis (NCC). However, information on the actual burden of this condition in NCC patients is limited and controversial. The few studies focusing on cognitive performance in NCC patients are heterogeneous regarding inclusion of patients with different forms of the disease, study design, and instruments used to assess cognition. A preliminary uncontrolled study in Brazil showed that 87.5% of NCC patients have cognitive impairment,[1] which is likely an overestimate. Subsequent controlled studies comparing cognitive performance across patients with different forms of NCC and persons with cryptogenic epilepsy or healthy individuals showed diverse results, ranging from no differences to significant impairment in some or all cognitive domains.[2–10]

Hippocampal atrophy is emerging as a rather frequent complication of NCC because of a diversity of mechanisms, including recurrent seizures (often subclinical) or recurrent bouts of inflammation related to periodic release of cysticercal antigens trapped within calcified cysticerci.[11] Given the major role of the hippocampus in memory and other cognitive functions, it is plausible to hypothesize that hippocampal atrophy could be the link to explain cognitive impairment in NCC patients. In addition, previous studies from our group have shown a significant association between NCC-related hippocampal atrophy and increasing age,[12] which, in turn, is also associated with worse cognitive performance. None of the aforementioned studies investigated the role of hippocampal atrophy or age to explain the cognitive performance of NCC patients compared with controls.[2–10]

The present study aimed to assess two questions: 1) Is there an association between calcified NCC and worse cognitive performance? 2) What is the relevance of hippocampal atrophy and age in this association?

The study was conducted in Atahualpa, a rural Ecuadorian village where NCC is endemic, and the population is homogeneous regarding race/ethnicity, living conditions, and dietary habits.[13,14] Using a population-based design, Atahualpa residents aged ≥ 40 years with NCC were identified as case patients and matched 1:1 by age and gender to individuals without evidence of NCC (control subjects), to compare cognitive performance by means of the Montreal Cognitive Assessment (MoCA) across groups. The Institutional Review Board (IRB) of Hospital-Clínica Kennedy, Guayaquil, Ecuador (Federal Wide Assurance [FWA] 00006867) approved the study.

Neuroimaging examinations were performed with a Philips Brilliance 64 computed tomography (CT) scanner and a Philips Intera 1.5T magnetic resonance imaging (MRI) machine (Philips Medical Systems, Eindhoven, The Netherlands), using previously defined protocols.[15] Women of childbearing age underwent a pregnancy test before CT, and subjects with contraindication for MRI were excluded. Neuroimaging examinations were read by a neurologist and a neuroradiologist blinded to clinical data and to each other assessment (discrepancies were resolved by consensus). Attention focused on the presence of lesions pathognomonic or highly suggestive of NCC.[16] In addition, hippocampi were rated using the Scheltens' medial temporal atrophy scale,[17] as previously described by our group.[12,15]

The Spanish version of the MoCA (www.mocatest.org, © Z. Nasreddine MD, version 07 November 2004) was used to assess cognitive performance. Montreal Cognitive Assessments were performed within 6 months of completion of neuroimaging studies. MoCA evaluates major cognitive domains: visuospatial executive, naming, attention and calculation, language, verbal abstraction, delayed recall, and orientation. Maximum MoCA score is 30 points, with an additional point given to persons with ≤ 12 years of education.[18]

Statistical analyses were carried out by using STATA version 15 (Stata Corporation, College Station, TX). In univariate analyses, prevalence of variables across case patients and controls were compared by the use of the McNemar's test for correlated proportions (matched pair analysis). A conditional logistic regression model adjusted for the level of education, history of recurrent epileptic seizures, symptoms of depression, and the presence of hippocampal atrophy was fitted for multivariate

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TABLE 1
Characteristics of case patients with calcified NCC and control subjects included in this study

	Total series (n = 158)	Case patients with NCC (n = 79)	Control subjects (n = 79)	Discordant pairs (n)	Pairs with only NCC exposed	Pairs with only control exposed	Significance
Age, years (mean ± SD)	61.7 ± 12.3	61.5 ± 12.3	61.9 ± 12.2	–	–	–	Matched
Women, n (%)	106 (67)	53 (67)	53 (67)	–	–	–	Matched
Primary school education, n (%)	85 (54)	44 (56)	41 (52)	19	11	8	OR: 1.38 95% CI: 0.50–3.94 P = 0.646
Recurrent seizures (epilepsy), n (%)	7 (4)	5 (6)	2 (3)	7	5	2	OR: 2.50 95% CI: 0.41–26.25 P = 0.449
Symptoms of depression, n (%)	19 (12)	9 (11)	10 (13)	15	7	8	OR: 0.88 95% CI: 0.27–2.76 P = 1.000
Hippocampal atrophy, n (%)	38 (24)	28 (35)	10 (13)	30	24	6	OR: 4.00 95% CI: 1.59–11.96 P = 0.002*

NCC = neurocysticercosis; OR = odds ratio; CI = confidence interval. Statistical significance of covariates across case patients and controls was calculated by the McNemar's test for paired data (univariate analyses).
* Statistically significant result.

analyses. Then, multivariate linear regression models were fitted to assess the importance of hippocampal atrophy and age in the association between calcified NCC and cognitive performance.

Of 863 Atahualpa residents aged ≥ 40 years identified during door-to-door surveys, 702 (81%) underwent a plain head CT. Of these, 83 (11.8%) had NCC. The only detected form of NCC was parenchymal brain calcifications, defined as rounded and homogeneous nonphysiological supratentorial calcifications, measuring < 1 cm in diameter, not associated with other neuroimaging findings suggestive of alternative etiologies, and not explained by any other causes.[16] Fifty-nine patients (75%) had a single parenchymal brain calcification, 16 (20%) had two to three calcifications, and the remaining four (5%) had ≥ 4 calcifications.

Four NCC patients did not undergo MRI (because of claustrophobia) and were excluded. MRI, performed in the remaining 79 (95%) of the 83 patients with NCC, did not detect any other type of cysticercotic lesion missed on CT with the exception of an old focus of gliosis surrounding one calcification.

Controls were selected from the 619 individuals without evidence of NCC on CT by the use of the Random integer generator (https://www.random.org/integers/). If a randomly selected individual did not match with the corresponding NCC patient or did not agree to participate, then, the next on the list (also matched by age and gender with the corresponding paired case patient) was chosen. MRIs were performed in all selected controls and did not identify any NCC lesions in these individuals.

Characteristics of participants are depicted in Table 1. As expected, the mean age and the percentage of women of case patients were similar to those of control subjects. By the use of the McNemar's test, there were no significant differences across groups regarding the level of education, history of recurrent epileptic seizures, or symptoms of depression. By contrast, 28/79 case patients (35%) and 10/79 controls (13%) had hippocampal atrophy (P = 0.002). The 38 participants with hippocampal atrophy were significantly older than those without atrophy (69.3 ± 10.2 versus 59.3 ± 11.9 years; P < 0.001), irrespective of their case/control status.

Table 2 shows the results of a conditional logistic regression model, adjusted for the aforementioned covariables. The model revealed no differences in the MoCA score across case patients and controls (P = 0.711). In this model, the single covariable remaining significant was the presence of hippocampal atrophy (P = 0.003).

In view of the results of the conditional logistic regression model, all participants (including case patients and controls) were stratified according to the presence of hippocampal atrophy. Unadjusted linear models showed a significant difference in the MoCA score across the 38 participants with hippocampal atrophy (irrespective of their case–control status) when compared with the 120 with normal hippocampi (19.9 ± 5.1 versus 22.5 ± 4.4; P = 0.003).

When mean values of the MoCA score were compared—in unadjusted analysis—across case patients with hippocampal atrophy (n = 28) versus those with normal hippocampi (n = 51), the MoCA score of case patients with hippocampal atrophy was significantly lower than those with normal hippocampi (19.9 ± 5.4 versus 22.9 ± 4; P = 0.006). However, the mean MoCA score of the 10 controls with hippocampal atrophy was not significantly different than that of the 69 controls without atrophy (20 ± 4.3 versus 22.2 ± 4.6; P = 0.158).

Because of the impact of increasing age in the association between calcified NCC and hippocampal atrophy,[12] a fully adjusted linear regression model including the 79 case patients was fitted (using the MoCA score as the dependent variable). In this model, age remained as the single significant covariate (Table 3).

Results of the models fitted for this study clearly answered the research questions. First, the conditional logistic regression model showed the importance of hippocampal

TABLE 2
Conditional logistic regression model (for matched paired data), showing no differences in the MoCA score across case patients and controls, but the significant contribution of hippocampal atrophy in this association

	Odds ratio	95% Confidence interval	P-value
MoCA score	0.98	0.88–1.09	0.711
Age (years)	0.66	0.43–1.01	0.055
Gender	1	–	–
Primary school education	1.62	0.53–4.92	0.393
Recurrent seizures (epilepsy)	3.58	0.54–23.8	0.187
Symptoms of depression	0.81	0.23–2.81	0.742
Hippocampal atrophy	4.35	1.62–11.7	0.003*

MoCA = Montreal Cognitive Assessment.
* Statistically significant result.

TABLE 3
Linear regression model (using the MoCA score as the dependent variable)

MoCA score	β-Coefficient	95% Confidence interval	*P*-value
Age (years)	−0.21	−0.31 to −0.12	< 0.001*
Gender	0.46	−1.52 to 2.45	0.645
Primary school education	0.77	−1.43 to 2.96	0.489
Recurrent seizures (epilepsy)	−0.98	−4.73 to 2.77	0.604
Symptoms of depression	0.11	−2.77 to 2.99	0.938
Hippocampal atrophy	0.51	−1.53 to 2.56	0.622

MoCA = Montreal Cognitive Assessment. The model only includes the 79 patients with calcified neurocysticercosis. The significance of hippocampal atrophy was lost, and age remained as the single significant covariate.
* Statistically significant result.

atrophy in the association between calcified NCC and cognitive impairment. Second, despite the age-matched characteristics of participants, those with hippocampal atrophy (case patients and controls) were significantly older than those without atrophy. Hippocampal atrophy resulted in lower MoCA scores only in case patients and not in control subjects. As a result, a multivariate linear regression model was fitted in case patients and showed that increasing age exerts a deleterious influence on cognitive performance among patients with calcified NCC-associated hippocampal atrophy.

The study has limitations. We relied on a single test to assess cognitive performance. However, MoCA has proven reliable for assessing cognitive performance in less educated individuals and has been correlated with structural brain damage documented by MRI in our population.[19] Neurocysticercosis diagnosis was based on the presence of "typical" calcifications, but it is theoretically possible—although unlikely—that other conditions may produce similar neuroimaging findings. The use of a visual scale for hippocampal atrophy rating could be seen as another potential limitation. However, reliability of the Scheltens' visual scale is comparable to that of volumetric assessment and is sufficient for estimating the severity of atrophy.[20] On the other hand, the strengths of the present study include the population-based design with unbiased selection of participants and the homogeneous characteristics of Atahualpa residents (including the fact that all case patients had the same form of NCC).

In summary, this study demonstrates an association between hippocampal atrophy and poor cognitive performance among patients with calcified NCC. Despite the lack of longitudinal information, biological plausibility suggests that the direction of the relationship seems to be from NCC to hippocampal atrophy and then to poor cognitive performance. In this postulated sequence of events, increasing age has an important effect, as showed in our study. Because about one-third of individuals with calcified NCC will eventually develop hippocampal atrophy after the age of 68 years,[12] this relationship is probably contributing to the burden of cognitive decline and dementia in older adults living in regions where NCC is endemic.

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