Calcified Neurocysticercosis and Headache in an Endemic Village: A Case–Control Study Nested to a Population-Based Cohort

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Abstract. Headache in patients with calcified neurocysticercosis (NCC) is probably common but has been largely overlooked. We aimed to assess the presence, characteristics, and diagnosis of headache across patients with calcified NCC and their matched controls. In this case–control study nested to a population-based cohort, Atahualpa residents aged ≥ 20 years with calcified NCC were identified as case patients and paired 1:1 to age- and gender-matched randomly selected controls. A culturally adapted questionnaire was derived from the EUROLIGHT. Headache diagnosis was established according to the International Classification of Headache Disorders, 3rd edition. Conditional logistic regression models for matched paired data were fitted to assess the independent association between calcified NCC (as the exposure) and headache variables, after adjusting for education, alcohol intake, depression, and epilepsy. The selection process generated 106 case patients and their matched controls. Lifetime headache prevalence (odds ratio [OR]: 4.18; 95% Confidence Interval [CI]: 1.79–9.75; $P = 0.001$), current headaches (OR: 4.19; 95% CI: 1.92–9.16; $P < 0.001$), and intense headaches (OR: 9.47; 95% CI: 2.88–31.19; $P < 0.001$) were more frequent among cases than in controls. In addition, migraine (but not other forms of headache) was more frequent among subjects with calcified NCC (OR: 4.89; 95% CI: 2.36–11.39; $P < 0.001$). This study shows a robust epidemiological association between headache—particularly migraine—and calcified NCC.

INTRODUCTION

Neurocysticercosis (NCC) is the most common helminthic infection of the nervous system and a major public health problem worldwide.¹ The disease occurs when humans become intermediate hosts in the life cycle of the tapeworm *Taenia solium*, after ingesting its eggs directly from a *Taenia* carrier or, less often, from the environment.² Population-based studies have confirmed that most infected individuals are asymptomatic,^{3,4} which is in contrast with the myriad of clinical manifestations observed in NCC patients attending neurological services.⁵ Most symptomatic patients present with seizures as the primary or sole manifestation of the disease.⁶ Others develop a combination of focal neurological signs, increased intracranial pressure, or cognitive decline, making NCC a pleomorphic disease. In this view, headache in patients with NCC has been largely overlooked or poorly characterized, and has been mostly reported in the context of an overt syndrome of intracranial hypertension related to cysticercotic encephalitis, hydrocephalus, or giant extraparenchymal cysts.^{7–9} Information on the association between calcified parenchymal brain cysticerci and headache is limited.^{10,11} Importance of accurate knowledge on this association comes from the traditional misconception that calcified cysticerci—probably the most frequent form of presentation of NCC—represent clinically inert lesions.¹² Using the Atahualpa Project cohort study, conducted in a rural village where calcified NCC has proven to be the only existing form of the disease,^{13–15} we aimed to assess the association between calcified NCC and headache by the use of a case–control study nested to this population-based cohort.

METHODS

Study population. The study was conducted in Atahualpa, a rural Ecuadorian village where NCC is endemic. Characteristics of Atahualpa residents have previously been described.¹⁶ In brief, the population is homogeneous regarding race/ethnicity, living conditions, socioeconomic status, and dietary habits. The village is closed, with a very low migration rate, which makes it an optimal setting for conducting population-based studies.

Study design. Using a population-based design, the study aimed to identify Atahualpa residents aged ≥ 20 years with NCC. Then, all consenting NCC cases were matched 1:1 by age (± 2 years) and gender to individuals without evidence of NCC (control subjects), to compare the presence, characteristics, and diagnosis of headache across groups by the use of conditional logistic regression models adjusted for relevant confounders (see in the following paragraph). The study followed the recommendations of the standards of reporting of neurological disorders guidelines¹⁷ and was approved by the Institutional Review Board of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867).

Identification of NCC cases. Steps for identifying subjects with NCC have been detailed elsewhere.^{13–15} In brief, all Atahualpa residents aged ≥ 20 years who provided signed informed consent were enrolled and referred for a non-enhanced computed tomography (CT) scan of the head. Women of child-bearing age underwent a pregnancy test before the study. Then, all cases identified as NCC on CT were offered a brain magnetic resonance imaging (MRI) (unless contraindicated) for better categorization of the lesions and to detect small viable lesions—mostly in the subarachnoid space—that could have been missed on CT. Examinations were performed by the use of a Philips Brilliance 64 CT scanner and a Philips Intera 1.5T MRI scanner (Philips Medical Systems, Eindhoven, The Netherlands), following predefined protocols.¹⁴ A neuroradiologist and a neurologist independently read all examinations with attention to the presence of lesions

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pathognomonic or highly suggestive of NCC.¹⁸ In particular, 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, were considered to be most likely of cysticercotic origin. Inter-reader agreement was excellent ($k = 0.92$) and disagreements were resolved by consensus. In addition, all other intracranial lesions were identified and noticed.

Selection of control subjects. Individuals with no evidence of NCC on CT were selected as controls by the use of the Random Integer Generator (<https://www.random.org/integers/>), and then matched 1:1 by age (± 2 years) and gender to patients with evidence of NCC on CT. For this selection, participants were ordered according to their unique seven-digit code used for enrollment in the Atahualpa Project. If a given 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.

Headache assessment. Two neurologists independently interviewed all NCC cases and control subjects (blinded to neuroimaging information and to each other's assessments) with the use of a semi-structured questionnaire to inquire about the presence and characteristics of headache in both study groups. The questionnaire was adapted from the EUROLIGHT, a widely used and validated headache questionnaire.¹⁹ The instrument was independently translated and back-translated from the original English version to Spanish by bilingual physicians from our group, and disagreements in translation were resolved by consensus. Then, the Spanish version was simplified and culturally adapted—including vernacular Spanish words used by local people—with the aid of Atahualpa's community leaders and rural doctors who had been working in the village. The final version (Supplemental file) was previously tested for feasibility in a sample of 50 apparently healthy individuals (who were not registered to participate in the present study).

We first inquired if the individual ever had headaches (lifetime prevalence), if headaches were present during the past year (current or past), and asked about the intensity of pain (a numeric pain-rating scale is part of the questionnaire). Thereafter, headache diagnosis was established according to the International Classification of Headache Disorders, 3rd edition.²⁰ According to this classification, the present study reached up to the second-digit level of headache diagnosis (i.e., migraine with aura and chronic tension-type headache). Because current guidelines do not allow to definitively classify headache associated with intracranial cysticercotic calcifications as a secondary headache (not scientifically documented evidence), headaches in both case patients and control subjects were initially considered primary unless another proven cause of secondary headache was found (i.e., headache attributed to epileptic seizures, traumatic brain injury, substance use or withdrawal, and psychiatric disorders) and classified phenomenologically.²⁰

Covariates investigated. The level of education, severity of alcohol intake, symptoms of depression, and history of recurrent seizures (epilepsy) were identified as confounding variables. Severity of alcohol intake was dichotomized in < 50 g/day and ≥ 50 g/day. Symptoms of depression were assessed by the depression axis of the depression-anxiety-stress

21 scale, a reliable field instrument that measures dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia.²¹ For epilepsy assessment, a neurology resident conducted face-to-face interviews to identify individuals with a suspected seizure disorder, departing from the field instrument developed and validated by Placencia et al.,²² and then, a neurologist confirmed the diagnosis by means of an interview and a neurological examination, as detailed elsewhere.¹⁴

Statistical analyses. Data analyses were carried out by using STATA version 15 (StataCorp., College Station, TX). In univariate analyses, continuous variables were compared by linear models and categorical variables by the McNemar's test for paired data (matched-pair analysis). Conditional logistic regression models were fitted to assess the independent association between the investigated headache variables and calcified NCC (as the exposure), after adjusting for the level of education, severity of alcohol intake, symptoms of depression, and history of recurrent seizures. Among patients with NCC, the relationship between the number of calcified lesions (single versus more than one) and the presence, characteristics, and diagnosis of headache was also evaluated. In the subset of patients with a single parenchymal brain calcification, correlation between the location of the calcification and headache was also assessed.

FIGURE 1. Flow diagram depicting the process of enrollment and the reasons for not including potentially eligible individuals at each step of the process.

RESULTS

Figure 1 is a flow diagram depicting the process of enrollment and the reasons for not including potentially eligible individuals at each step of the enrollment process. Of 1,685 Atahualpa residents aged ≥ 20 years identified during yearly door-to-door surveys (2012–2017), 1,273 (76%) underwent a head CT. Of these, 121 (9.5%) had calcified NCC and the remaining 1,152 had no evidence of NCC on CT. MRI was performed in 110 (91%) of the 121 with NCC and did not detect any other type of cysticercotic lesion missed on CT with the possible exception of an old focus of gliosis surrounding one calcified lesion. MRIs were also performed—for other research purposes—in 384 (33%) of the 1,152 individuals without NCC on CT. Likewise, MRIs did not identify new NCC cases among those with a negative CT scan.

Seven of the 121 patients with NCC died between the time the CT was performed and the subsequent headache interview (from causes apparently not related to NCC), one had left the village, four refused further participation, and three were excluded because neuroimaging studies showed other lesions potentially associated with headache (a congenital arachnoid cyst in the temporal lobe, a convexity meningioma, and a colloid cyst of the third ventricle). This left 106 case patients with calcified NCC for analysis.

Thirty-one of the 1,152 NCC-free individuals had died and 15 had left the village by the time of the subsequent interview. Therefore, the Random Integer Generator calculated controls on the basis of the remaining 1,106 individuals. Of the 106 subjects initially selected as controls, 31 did not match to NCC patients, four presented with intracranial lesions potentially associated with headache (an old putaminal hemorrhage, a clipped intracranial aneurysm, a parenchymal cavernous angioma, and a hemangioma of the diploe), and five declined the interview. These 40 subjects were substituted with corresponding subjects next on the list (as detailed previously).

The mean age of the 106 NCC patients was 51 ± 16.8 years (median age: 51 years; age range: 21–87 years), and 70 (66%)

were women. As expected, these numbers were similar to those of control subjects (mean age 51 ± 16.9 years [median age: 51 years; age range: 21–88 years], and 66% women). Among case patients with NCC, 48 (45.3%) had primary school education only, 21 (19.8%) disclosed alcohol consumption ≥ 50 g/day, six (5.7%) had symptoms of depression, and eight (7.5%) had epilepsy. Among the 106 controls, 46 (43.4%) had primary school education only, 17 (16%) disclosed alcohol consumption ≥ 50 g/day, nine (8.5%) had symptoms of depression, and only one (0.9%) had epilepsy.

A total of 148 of the 212 participants (69.8%) ever had headaches, 103 (48.6%) had current headaches, and 60 (28%) had intense headaches (≥ 7 in the numeric pain-rating scale). In the 106 case patients with NCC, 87 (82.1%) ever had headaches, 66 (62.3%) had current headaches, and 46 (43.4%) had intense headaches. Among the 106 control subjects, 61 (57.6%) ever had headaches, 37 (34.9%) had current headaches, and 14 (13.2%) had intense headaches (Figure 2).

Table 1 shows the characteristics of the study population across case-control status. Using the McNemar's test for paired data, the single covariate achieving significance in the univariate analysis between case patients and controls was the presence of epilepsy ($P = 0.045$), which was expected because of the well-known association between NCC and epilepsy.¹⁴ Also, in univariate analyses, lifetime headache prevalence ($P < 0.001$), presence of current headaches ($P < 0.001$), and intense headaches ($P < 0.001$) were significantly more common in case patients with NCC than in controls.

Conditional logistic regression models, adjusted for the aforementioned confounders, also revealed significantly increased lifetime headache prevalence (OR: 4.18; 95% Confidence Interval [CI]: 1.79–9.75; $P = 0.001$), current headaches (OR: 4.19; 95% CI: 1.92–9.16; $P < 0.001$), and intense headaches (OR: 9.47; 95% CI: 2.88–31.19; $P < 0.001$) among case patients with NCC than in control subjects. None of the included covariates remained significant in these multivariate models.

FIGURE 2. Graph showing percentages (with 95% confidence intervals) of ever, current, and intense headaches across case patients with neurocysticercosis and controls.

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

	Total series (N = 212)	Case patients with NCC (N = 106)	Control subjects (N = 106)	Significance
Age, years (mean $\pm$ SD)	51 $\pm$ 16.8	51 $\pm$ 16.8	51 $\pm$ 16.9	Matched
Women, n (%)	140 (66)	70 (66)	70 (66)	Matched
Primary school education, n (%)	94 (44.3)	48 (45.3)	46 (43.4)	OR: 1.15 95% CI: 0.60–2.21 P = 0.760
Alcohol intake $\geq$ 50 g/day, n (%)	38 (17.9)	21 (19.8)	17 (16)	OR: 1.5 95% CI: 0.56–4.2 P = 0.502
Symptoms of depression, n (%)	15 (7)	6 (5.7)	9 (8.5)	OR: 0.67 95% CI: 0.19–2.09 P = 0.606
Recurrent seizures (epilepsy), n (%)	9 (4.2)	8 (7.5)	1 (0.9)	OR: 8 95% CI: 1.07–354.9 P = 0.045
Ever had headaches, n (%)	148 (69.8)	87 (82)	61 (57.5)	OR: 4.25 95% CI: 1.93–10.63 P < 0.001
Current headaches, n (%)	103 (48.6)	66 (62.2)	37 (34.9)	OR: 3.90 95% CI: 1.91–8.76 P < 0.001
Intense headaches, n (%)	60 (28.3)	46 (43.3)	14 (13.2)	OR: 6.5 95% CI: 2.73–18.79 P < 0.001

CI = confidence interval; NCC = neurocysticercosis; SD = standard deviation. Statistical significance was calculated by the McNemar's test for paired data (univariate analyses).

Based on the criteria of the International Classification of Headache Disorders, 3rd edition,²⁰ 145/148 had primary headaches and the remaining three had secondary headaches (two had headaches related to the use of or exposure to a substance, and the other had headache attributed to epileptic seizures). Among the 145 individuals with primary headaches, 95 (65.5%) had migraine and 50 (34.5%) had tension-type headache. The most frequent type of migraine was migraine without aura (N = 53), followed by probable migraine (N = 39), migraine with aura (N = 9), chronic migraine (N = 3), and complications of migraine (N = 1). The most common type of tension-type headache was infrequent episodic tension-type headache (N = 42), followed by frequent episodic tension-type headache (N = 4), probable tension-type headache (N = 3), and chronic tension-type headache (N = 1).

Among the 87 case patients with NCC who reported headache, migraine was the most common diagnosis (N = 65; 74.7%), followed by tension-type headache (N = 19; 21.8%) and secondary headaches (N = 3; 3.5%). Among the 61 control subjects who reported headache, 30 (49.2%) had migraine and the remaining 31 (50.8%) had tension-type headache. By the use of the McNemar's test, migraine was more frequent among case patients with NCC than in control subjects (OR: 4.89; 95% CI: 2.36–11.39; $P < 0.001$), but there was no significant difference in subjects with tension-type headache across case patients and controls (OR: 0.52; 95% CI: 0.24–1.06; $P = 0.074$).

A total of 173 supratentorial parenchymal brain calcifications were seen in the 106 cases with NCC. Of these, 75 (71%) had a single calcification, 25 (23%) had from two to three calcifications, and the remaining six (6%) had ≥ 4 calcifications. Calcifications were most often located in the parietal lobe (N = 66), followed by the frontal (N = 36), the occipital (N = 34), and the temporal lobes (N = 26); the remaining 11 calcifications were located deep in the brain (basal ganglia or thalamus). When comparing the investigated headache variables in patients with a single versus in those with more than one calcification, there were no differences in the prevalence of lifetime headache

($P = 0.174$), current headache ($P = 0.311$), intense headaches ($P = 0.845$) or migraine prevalence ($P = 0.658$) across groups. Likewise, the location of the intracranial calcification (in 75 patients with a single lesion) had no relationship with the investigated headache variables, with the exception of temporal lobe calcifications, which were more frequently associated with migraine ($P = 0.01$) than calcifications in other sites.

DISCUSSION

In this case-control study nested to a population-based cohort, conducted in a village endemic for NCC, persons with headache had increased odds of having calcified NCC than those without headache, providing robust epidemiological evidence favoring the association between calcified NCC and headache. Association found in a cross-sectional study does not imply causation. Nevertheless, biological plausibility suggests a cause-and-effect relationship between calcified NCC as the exposure and headaches as the outcome because the opposite is unlikely and there were no other apparent confounders that explain the outcome.

As previously noted, evidence of a relationship between calcified NCC and headache is limited. In one study conducted in a small rural village located in the Andean region of Ecuador, CT showed calcified NCC in 15/57 (26.3%) patients with migraine and in 14/109 (12.8%) nonmatched asymptomatic individuals ($P = 0.03$).¹⁰ In a clinical series involving 7,519 individuals attending a large hospital in Guayaquil (Ecuador) over 20 years, calcified NCC was significantly more frequent among patients consulting for "primary headache" than among those with cerebrovascular disease, degenerative disorders of the central nervous system, and head trauma.¹¹ To our knowledge, these are the only studies that specifically address the association between calcified NCC and headache and both were compromised by selection bias, one because of the small sample size and the unmatched selection of controls¹⁰ and the other because it focused on patients consulting a neurological

service not representative of the population at large.¹¹ Although the design of the present study differs from those of these prior reports, all serve to suggest a relationship between calcified NCC and headache.

Of special interest is the finding that migraine is over-represented among case patients with headache when compared with controls. Mechanisms involved in the pathogenesis of calcified NCC-related migraine appear to be complex. Calcified lesions represent the end stage of cysticerci destroyed by either the host immune system or as the result of cysticidal drug therapy. Neuroimaging and histopathological studies have shown that calcified cysticerci contain remnants of antigenic parasitic membranes, which are periodically exposed to the host immune system as the result of morphological changes in the calcifications related to remodeling mechanisms.^{23–25} This exposure causes inflammatory changes in the neighboring brain parenchyma with the subsequent breakdown in the blood–brain barrier, edema formation, and liberation of free radicals including nitric oxide.^{26,27} The oxidative stress upregulates the liberation of the calcitonin gene-related peptide and other substances from central neurons, which—in turn—stimulates the trigemino-vascular reflex, causing a migraine attack.^{28–30} To add complexity to this proposed sequence of events, it has been shown that the calcitonin gene-related peptide downregulates inflammation and stabilizes the blood–brain barrier, thus controlling inflammation.³¹ In this view, pathophysiological mechanisms triggering a migraine attack may also be seen as protective for the brain damage induced by inflammation and enhanced oxidative stress.³²

The previously described sequence of events would explain why migraine—but not other forms of headache, such as tension-type headache—was more frequent among NCC patients than among control subjects in the present study.

The sub-analysis of headache across NCC patients with a single versus more than one parenchymal brain calcifications showed that the burden of infection has no significant relationship with the outcome. This suggests that antigenic stimuli coming from a single calcification might be sufficient to induce episodes of headache by the aforementioned pathogenetic mechanisms. On the other hand, we found a significant association between the presence of temporal lobe calcifications and migraine attacks. These results are in line with the previous work showing that the temporal lobe plays a role in the pathophysiology of migraine,³³ a finding that deserves further study.

Major strengths of this study include the unbiased selection of participants, the systematic procedures used for the identification of case patients and their matched control subjects, the assessment of headache by certified neurologists using a validated questionnaire together with the current international classification of headache disorders, and the statistical models fitted to analyze data.

The study has limitations. First, we based the diagnosis of NCC on the presence of “typical” calcifications,¹⁸ but it is theoretically possible—although unlikely—that other infectious or noninfectious conditions may produce similar neuroimaging findings. Second, we cannot rule out the presence of some hidden confounders that might have influenced our results. Third, we did not measure the calcitonin gene-related peptide in peripheral blood, which is considered a potential biomarker of migraine.³⁴ This may have provided more insight into the mechanisms involved in the pathogenesis of calcified NCC-related migraine. Fourth, we did not

perform lumbar punctures to compare the presence of byproducts of inflammation in the cerebrospinal fluid across NCC patients with and without headache (particularly among those with current headaches).²⁷ In addition, only 33% of NCC-free individuals on CT underwent a brain MRI, and it could be argued that an MRI is more sensitive for detecting small viable NCC lesions not detected by CT, thus limiting the reliability of our findings. However, the lack of additional NCC lesions seen in MRIs performed in 91% of patients with CT evidence of calcified NCC, together with the recent demonstration that NCC transmission had spontaneously arrested in Atahualpa, makes this possibility highly unlikely.¹⁵ Immune tests (such as the enzyme-linked immunoelectrotransfer blot assay) for confirming the diagnosis of NCC in CT-positive cases were not performed. However, all NCC cases were in the calcified state and this is not an appropriate population to assess the performance of antibody serology because only a small proportion of them will test positive.³⁵

It may also be argued that some NCC patients reinfect between the time of the CT and the headache interview, and this could have been associated with symptoms that were not present at the time when they only had calcified NCC in the brain. However, this possibility is remote because all individuals enrolled in the Atahualpa Project are under continuous surveillance by our field personnel, and every time they develop relevant clinical manifestations, they are examined again by neurologists and underwent repeated neuroimaging studies if necessary. In addition, a survey conducted during the past year revealed no infected pigs in the village and no evidence of active infections in Atahualpa residents with calcified NCC by the use of a monoclonal antibody-based enzyme-linked immunosorbent assay aimed to detect *T. solium* antigens in urine.¹⁵ It can also be argued that patients with known calcified NCC were more prone to respond positively to some questions of the headache questionnaire than those who know that their CT is normal. However, it is highly unlikely that the responses were directed to the diagnosis of a specific headache subtype (migraine), which was almost five times more frequent among NCC patients than among controls.

In conclusion, this study demonstrates a robust relationship between calcified NCC and headache in a village endemic for NCC. This relationship is likely to exist in many similar endemic regions, where calcified NCC is a probable factor contributing to the global burden of headache. Longitudinal—preferably multicentric—studies are needed to determine whether a causal relationship between calcified NCC and migraine attacks exists, to characterize the pathogenetic mechanisms involved, and to identify potential biomarkers of headache in these patients.

Received April 12, 2018. Accepted for publication May 20, 2018.

Published online June 25, 2018.

Note: Supplemental file appears at www.ajtmh.org.

Financial support: This study was partly supported by Universidad Espíritu Santo, Ecuador.

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