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Epilepsy, interictal EEG abnormalities and hippocampal atrophy in patients with calcified neurocysticercosis: a population study in an endemic milieu

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ABSTRACT

Objective. Calcified neurocysticercosis has been associated with hippocampal atrophy (HA). However, the pathogenesis of this association is still elusive. This study assessed the role of epilepsy or interictal EEG abnormalities in the occurrence of HA in the Atahualpa Project cohort.

Methods. Atahualpa residents aged ≥20 years, identified by means of door-to-door surveys, were offered an unenhanced head CT to identify neurocysticercosis cases. Individuals with cysticercotic parenchymal brain calcifications (121/1,299; 9.3%) underwent brain MRI, scalp EEG, and neurological evaluation to assess history of epilepsy. The independent association between combined exposures (epilepsy and/or EEG abnormalities) and HA (outcome) was assessed using univariate logistic regression models and a multivariate model adjusted for age, sex, level of education, alcohol intake and characteristics of calcifications.

Results. A total of 112 NCC patients were enrolled (mean age: 52.2 ± 16.9 years; 67% women); the remaining nine declined consent. A single calcification was noticed in 70% of cases. Thirty-one patients (27.7%) had HA, which was asymmetrical in 14. Calcification burden was higher among patients with HA than in their non-atrophic counterparts (p=0.012). Eighteen patients had epilepsy, abnormal EEG recordings, or both. Nine of these 18 patients (50%) had HA as opposed to 22 of 94 patients (23%) with a normal EEG and no history of epilepsy (p=0.025). This association became borderline significant based on a multivariate logistic regression model, after adjusting for all covariates (OR: 3.26; 95% CI: 0.91-11.68; p=0.070). In this model, having only one calcification was inversely associated with HA (OR: 0.32; 95% CI: 0.11-0.95; p=0.039).

Significance. Epilepsy and EEG abnormalities play a minor contributory role in the development of HA in neurocysticercosis patients. The burden of infection, leading to recurrent bouts of inflammation around calcified cysticerci, is a more likely contributor to HA development in patients with neurocysticercosis.

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Neurocysticercosis (NCC), the most frequent helminthic infection of the nervous system, is a leading public health problem in the developing world as well as in several developed countries with a high influx of immigrant population from endemic areas [1]. While in many cases, NCC remains asymptomatic for the lifespan of infected individuals, a sizable proportion of patients develop significant neurological morbidity [2]. Epilepsy is the most common form of presentation of the disease, occurring in about two-thirds of symptomatic cases, mostly when cysticerci are located in the brain parenchyma [3-5]. These parasites, particularly when they transform into granular nodules or calcifications, establish as enduring epileptogenic foci that are the cause of recurrent unprovoked seizures [6].

Lack of correlation between the location of brain parasites and seizure semiology (observed in several cases) has led some authors to hypothesize that both epilepsy and NCC may occur by chance [7]. While this is theoretically possible, the bulk of evidence suggest a causal relationship between NCC and epilepsy, including the higher prevalence of epilepsy in NCC endemic areas when compared with non-endemic regions and the observance of inflammatory changes surrounding calcified cysticerci immediately after a seizure in roughly half of these patients [8, 9]. In addition, several studies have shown that up to one third of patients with NCC also develop secondary hippocampal atrophy (HA), which may be a substrate for the occurrence of seizures and may represent the missing link for cysticercosis epileptogenesis in patients with incongruence between the location of parasites and seizure semiology [10-13].

Whether HA in NCC patients is related to recurrent seizures or to periodic inflammation from a distant calcification is still under debate. A major problem in most studies attempting to solve this question is that clinical interviews may underestimate the prevalence of epilepsy in NCC-endemic areas [14]. Moreover, most studies have not taken into account the information provided by EEG, which may disclose subclinical epileptiform or encephalopathic activity in NCC patients without evidence of epilepsy. A previous case-control study conducted by our group suggested that seizures were a minor contributor to the prevalence of HA in NCC patients. Limitations of that study were the small sample size together with the low prevalence of interictal epileptiform or encephalopathic activity in the studied population [15].

Based on the well-established Atahualpa Project cohort, this study aimed to expand the sample size of our previous study by evaluating a larger series of patients with calcified parenchymal brain cysticerci – investigated by CT, MRI and EEG – to settle the role of epilepsy or interictal EEG abnormalities in the occurrence of HA.

Methods

Study population

Atahualpa is a rural village located in coastal Ecuador where previous epidemiological studies have demonstrated the endemicity of NCC [9, 12, 13, 16]. The population of Atahualpa is homogeneous regarding race/ethnicity, lifestyles and socio-economic status [17]. Domestic pig raising is common; however, the vast majority of pigs were negative when tested with the enzyme-linked immunotransfer blot assay for the detection of *T. solium* antibodies, suggesting a spontaneously arrested transmission of the disease complex Taeniasis/cysticercosis in the village, and explaining why all people with NCC have calcifications only [18].

Study design

All subjects aged ≥20 years enrolled in the Atahualpa Project cohort were offered an unenhanced CT of the head, and those who consented were eligible for enrollment. Women of childbearing age had a pregnancy test before the CT scan and those who were pregnant were re-scheduled after delivery. Individuals whose CT showed NCC-related calcifications were offered a scalp EEG and a brain MRI, and those who underwent both procedures were enrolled. Univariate and multivariate models were used to assess the association between EEG abnormalities, history of epilepsy, and HA. The study followed the recommendations of the standards of reporting of neurological disorders (STROND) guidelines [19], and both the study protocol and a comprehensive informed consent were approved by the I.R.B. of our Institution (FWA: 00028878).

Clinical interviews

All individuals were interviewed by trained field personnel to assess demographics, level of education, and alcohol intake. Most NCC patients with epilepsy or history of a single seizure have been previously identified by our group, based on a validated field instrument to identify suspected cases [20], and a subsequent neurological interview to confirm the diagnosis [9]. Nevertheless, all enrolled individuals were again evaluated by a certified neurologist to update their medical records and to assess the existence of new persons with epilepsy (PWE) or the occurrence of incident seizures among those already identified.

Neuroimaging protocol

CT and MRI were performed with a Philips Brilliance 64 CT scanner and a Philips Intera 1.5T MR scanner (Philips Medical Systems, Eindhoven, the Netherlands), as previously detailed [9, 12]. All examinations were independently interpreted by a neurologist and a neuroradiologist. Based on CT, rounded and homogeneous non-physiological supratentorial calcifications, measuring <1 cm in diameter, and not explained by any other alternative etiology, were considered to be of cysticercotic origin [21]. The number and location of calcifications were noted. Inter-reader agreement was excellent (k=0.92) and disagreements were resolved by consensus. On MRI, a T1-weighted inversion recovery sequence oriented in the coronal plane and perpendicular to the long axis of the temporal bone was used for hippocampal evaluation. Hippocampi were rated using the Scheltens' medial temporal atrophy scale [22], which grades the width of the choroid fissure and the temporal horn, as well as the height of the hippocampus on a 5-point rating scale, ranging from no atrophy (0 points) to severe atrophy (4 points). Up to 1 point for persons <75 years of age, and 2 points for persons ≥75 years were considered age-related changes. Each temporal lobe was rated separately, and any asymmetry ≥1 point was noted. Kappa coefficients for inter-rater agreements were 0.85 for any HA; discrepancies were resolved by consensus.

EEG recordings and interpretation

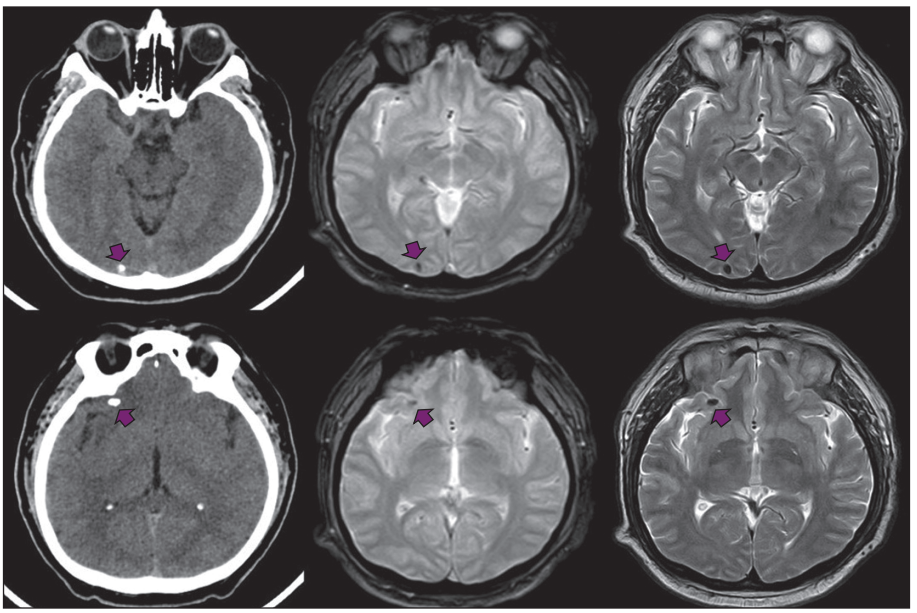
One-hour scalp EEGs were performed using a Nihon Kohden EEG-1200 digital machine (Nihon Kohden Corporation, Tokyo, Japan) and collected using the international 10-20 electrode configuration, with the addition of T1 and T2 electrodes, as detailed elsewhere [15]. Studies included eye opening, eye closure, hyperventilation, photic stimulation, wakefulness, and sleep (when possible). All examinations were reviewed by an epilepsy board-certified neurologist, blinded to clinical data and neuroimaging findings. The severity of encephalopathy (mild, mild-to-moderate, or moderate) was calculated according to the background frequency, the presence of background attenuation, lack of reactivity to eye opening, and intermittent generalized slowing [23].

Statistical analyses

Data analyses were carried out using STATA version 16 (College Station, TX, USA). Based on univariate analyses, continuous variables were compared by linear models and categorical variables by x^2 or the Fisher exact test, as appropriate. The independent association between the presence of two combined independent variables (an abnormal EEG and/or history of epilepsy) and HA (as the dependent variable) was assessed by fitting a multivariate logistic regression model adjusted for age, sex, level of education, alcohol intake, and the burden of calcified NCC lesions.

Results

From a total of 1,299 Atahualpa residents aged ≥20 years who underwent a CT scan of the head, 121 had NCC (9.3%; 95% CI: 7.9-11%). Patients with NCC were older (53.3 ± 17 versus 47.3 ± 18.5 years; p<0.001), more often women (65% versus 53%; p=0.009) and more often had epilepsy (7.4% versus 2.5%; p<0.001) than those without NCC. There were no differences in the level of education, alcohol intake, or history of a single seizure across subjects with and without NCC.
Nine of the 121 patients with NCC did not undergo either brain MRI or an EEG, and so were excluded from analysis (coverage: 92.6%). The mean age of the 112 participants was 52.2 ± 16.9 years (median age: 51.5 years), 75 (67%) were women, 51 (46%) had primary school education only, 20 (18%) disclosed heavy alcohol intake, eight (7%) had epilepsy, and two (1.6%) had history of a single seizure. Individuals with a single seizure were not considered as PWE.
In the eight subjects with epilepsy, the mean age at the first seizure was 25.6 ± 20 years (age range: 2-62 years). The mean (±SD) duration of epilepsy was 31 ± 18.2 years. No PWE had a family history of epilepsy. Three PWE had fewer than five seizures, one had between six and 10, and the remaining four recalled more than 20 lifetime seizures. Four subjects had active epilepsy, *i.e.* had at least one seizure in the past year, were taking anti-seizure medication, or both. Seizures included generalized tonic-clonic convulsions in five cases and were exclusively focal in three. None of these eight patients had temporal lobe epilepsy. All PWE had a normal neurological examination.
As previously described, all NCC patients in Atahualpa had calcified lesions in the brain parenchyma, and there were no cases with active forms of the disease or extraparenchymal lesions [9, 18]. These calcifications occurred as the result of the immune attack from the host, as no patient had been treated with cysticidal agents. Other lesions identified by CT were a small convexity meningioma and a congenital subarachnoid cyst in the temporal lobe (neither patients had a history of a seizure disorder).
CT showed a total of 187 calcifications, with a mean (±SD) of 1.7 ± 1.7 calcifications per person. Seventy-eight patients (70%) had a single calcification,



■ **Figure 1.** Unenhanced CT scans showing parenchymal brain calcified cysticerci located in the right temporal and occipital lobes from one subject (left panel). On MRI, these lesions appear as signal void lesions in both gradient-echo (686/23) and T2-weighted (4500/100) sequences (center and right panels, respectively).

29 (26%) had from 2-4 calcifications, and the remaining five (4%) had ≥five calcifications. Calcifications were located in the left cerebral hemisphere in 45 cases, in the right hemisphere in 45, and in both hemispheres in the remaining 22. There were no calcifications in the posterior fossa. The parietal lobes were most frequently affected (77 calcifications), followed by the frontal (n=46), the occipital (n=35), and the temporal lobes (n=18). The remaining calcifications (n=11) were located deep in the brain (basal ganglia or thalami).

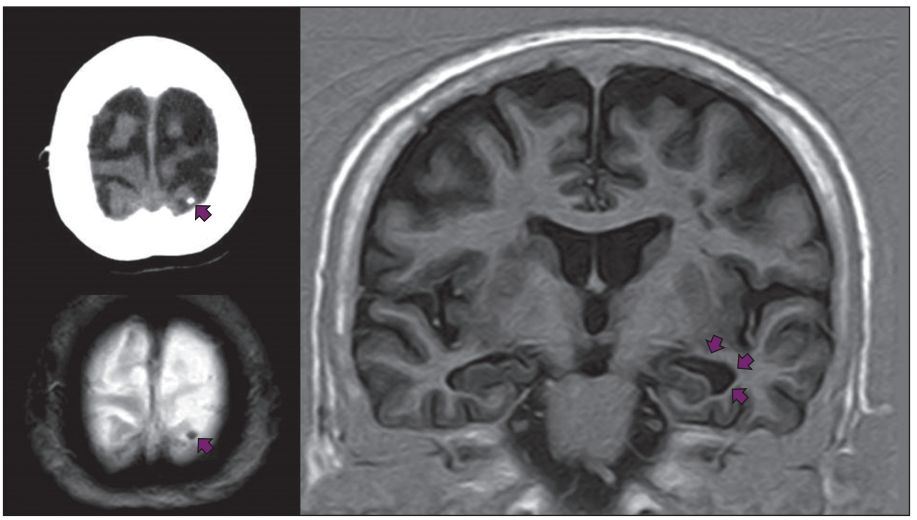
MRI identified the calcifications in about 60% cases, particularly using the T2-weighted and gradient-echo sequences, in which they appeared as small signal void lesions (*figure 1*). MRI did not detect any lesions missed on CT except for an earlier focus of gliosis adjacent to one calcification and neuroimaging signatures of cerebral small vessel disease in some cases, particularly in older adults [24]. Likewise, MRI did not identify new NCC cases among those with a negative CT scan.

Thirty-one patients (27.7%; 95% CI: 20.2-36.6%) had HA, which was asymmetrical in 14. In 12 (86%) patients with asymmetric HA, there was at least one calcification located in the same cerebral hemisphere (*figure 2*). Patients with HA were older (63.6 ± 15.4 versus 47.8 ± 15.2 years; $p<0.001$), and more often had epilepsy than those without atrophy, although the difference did not reach significance (13% versus 5%; $p=0.143$). In addition, the mean (±SD) number of calcifications was significantly higher among patients with HA than in their non-atrophic counterparts (2.3 ± 2.9 versus 1.4 ± 0.8; $p=0.012$). On the other hand, the location of calcifications in the different cerebral lobes did not differ across patients with and without atrophy (data not shown).

A total of 13 patients (11.6%; 95% CI: 6.9-18.9%) had an abnormal EEG, which showed epileptiform activity in three, a diffuse encephalopathic pattern in nine, and both abnormalities in one case. Of the four patients with epileptiform activity, two had only one calcification, one had three, and the remaining had six. Diffuse encephalopathic abnormalities were mild in seven cases and mild-to-moderate in the remaining three.

Based on univariate analyses, there were no demographic differences nor disparities in the burden of calcifications across patients with a normal or abnormal EEG. In contrast, patients with an abnormal EEG more often had epilepsy and HA than those with a normal EEG. Also based on univariate analysis, PWE were less educated and more often had an abnormal EEG than those without epilepsy (*table 1*).

A total of 18 patients had either an abnormal EEG (n=10), history of epilepsy (n=5), or both (n=3). Nine of these 18 patients (50%) had HA as opposed to 22 of 94 patients (23%) with a normal EEG and no history of epilepsy (OR: 3.27; 95% CI: 1.16-9.26; $p=0.025$). However, the significance of this association became borderline based on a multivariate logistic regression model, after adjusting for all of the above-mentioned covariates (OR: 3.26; 95% CI: 0.91-11.68; $p=0.070$).



■ **Figure 2.** Unenhanced CT and gradient-echo (686/23) MRI (left panel) showing a single parenchymal brain calcification in the left occipital lobe (arrow), and T1-weighted inversion recovery MRI sequence (right panel) showing asymmetric hippocampal atrophy, more marked on the left (arrows).

In this model, HA was directly associated with increasing age and inversely associated with having only one cysticercotic calcification (*table 2*).

Discussion

While the association between NCC, HA and temporal lobe epilepsy has been extensively demonstrated in hospital-based studies evaluating patients with intractable epilepsy [11, 25], pathogenetic mechanisms involved in this association are still elusive. It has been postulated that HA could develop in response to recurrent seizures generated by NCC lesions, or that it results from recurrent bouts of inflammation related to periodic release of trapped antigens located inside calcified NCC lesions [26-28].

This population study, conducted in community dwellers with calcified NCC, showed, based on univariate analysis, a significant association between epilepsy and/or EEG abnormalities on one hand and HA

▼ **Table 1.** Characteristics of NCC patients across epilepsy status and EEG findings (univariate analyses).

Variable	Total series (*n*=112)	Epilepsy status			EEG findings		
		No epilepsy (*n*=104)	Epilepsy (*n*=8)	*p* value	Normal EEG (*n*=99)	Abnormal EEG (*n*=13)	*p* value
Age, years (mean±SD)	52.2 ± 16.9	51.8 ± 16.7	56.6 ± 19.2	0.440	51.2 ± 16.3	59.5 ± 19.8	0.095
Women, *n* (%)	75 (67)	70 (67)	5 (63)	0.718	65 (66)	10 (77)	0.539
Primary school education, *n* (%)	51 (46)	44 (42)	7 (88)	0.022*	42 (42)	9 (69)	0.082
Heavy alcohol intake, *n* (%)	20 (18)	19 (18)	1 (13)	0.681	20 (20)	0	...
Calcifications per person (mean±SD)	1.7 ± 1.7	1.7 ± 1.8	1.4 ± 0.7	0.641	1.7 ± 1.8	1.5 ± 1.4	0.701
Hippocampal atrophy, *n* (%)	31 (28)	27 (26)	4 (50)	0.214	24 (24)	7 (54)	0.025*
Epilepsy, n (%)	8 (7)	...	...	...	5 (5)	3 (23)	0.049*
EEG abnormalities, *n* (%)	13 (12)	10 (10)	3 (38)	0.049*	...	...	...

*Statistically significant result.

▼ **Table 2.** Results of a multivariate logistic regression model in 112 patients with calcified neurocysticercosis showing associations with hippocampal atrophy as the dependent variable.

	Hippocampal atrophy			
	Odds ratio	**Standard error**	**95% CI**	***p* value**
Epilepsy/abnormal EEG	3.26	2.12	0.91 – 11.7	0.070
Age, years (mean±SD)	1.07	0.02	1.03 – 1.12	<0.001*
Female gender	0.58	0.38	0.16 – 2.11	0.411
Primary school education	0.83	0.51	0.25 – 2.76	0.764
Heavy alcohol intake	0.63	0.54	0.12 – 3.35	0.585
Presence of a single calcification	0.32	0.18	0.11 – 0.95	0.039

*Statistically significant result.

on the other, but this association was no longer significant after taking into account the effect of covariates. Nevertheless, the multivariate model showed that the odds of having HA was more than three-fold higher among patients with epilepsy and/or EEG abnormalities, suggesting a role of clinical or subclinical seizure activity in the occurrence of HA. Interestingly, having only one cysticercotic calcification was inversely associated with HA in the multivariate model, suggesting that the burden of calcifications also plays a role in the development of hippocampal damage. Results of the present study provide further support to previous investigation suggesting that HA in patients with NCC may develop through multiple pathogenetic mechanisms, with seizures and EEG abnormalities being only contributory [15, 27-29].

The prevalence of HA in patients enrolled in the present study was 27.7% (31 out of 112). Excluding the nine patients who had abnormal EEG and/or history of epilepsy, the prevalence of HA was 23% in the remaining individuals (22 out of 94), which is still higher than the average percentage of HA found in the general population (without NCC) [30-32]. Assuming a scenario in which some subclinical epileptiform activity is missed on scalp EEGs [33, 34], and that some patients fail to recall a history of seizures [35], there is still a gap in the percentage of HA in patients with NCC when compared to that of the population at large. Thus far, the most likely explanation for such disparity is inflammation-related hippocampal damage in patients with NCC, which occurs irrespective, and often in the absence of seizures [36].

Neuroimaging as well as pathological studies have demonstrated the presence of parasitic remnants in the interior of NCC-related calcifications, changing the previous concept that calcifications are totally inactive and solid nodules [37-39]. In these cases, periodic remodeling of calcifications may expose trapped antigens to the host's immune system, which may account for recurrent inflammatory events that trigger HA, not necessarily associated with seizures. It can be argued that the more calcifications in the brain parenchyma, the higher the possibility that trapped antigens become exposed to the host's immune system and, consequently, the greater the risk for HA to develop. The results of the present study are in line with this hypothesis, with a significant inverse association between the presence of a single calcification (as opposed to more than one lesion) and HA.

Clinical and experimental studies have provided additional support to the possibility of inflammation-mediated HA in NCC patients. It has been argued that if inflammation related to NCC leads to HA, the development of atrophy would occur several years after the infection [27]. This hypothesis is consistent with the findings of a population-based case-control study demonstrating that HA was more prevalent only in older patients with NCC than in control subjects [13]. Also, in the present study, increasing age was significantly associated with HA in the multivariate model. In addition, repeated endotoxin exposure and increased levels of pro-inflammatory cytokines correlate with hippocampal damage in mice independent of seizures [40]. More recently, using a rat model of *Taenia solium* cysticercosis, axonal swelling with spheroid formation was found quite distant from cysticerci [41]. These axons originated from neurons located near cysticerci, and the cell bodies were damaged as the result of inflammation around parasites. It is possible that many of these damaged axons end either in the hippocampi themselves or in distant areas that project to hippocampi, resulting in deafferented hippocampi, which, in turn, provide a substrate for the development of HA [42].

The lack of a control group (individuals without NCC) is a limitation of this study. However, differences in the prevalence and correlates of HA across individuals with and without NCC have previously been demon-

strated in the study population [12, 13, 15]. The present study focused on differences in the characteristics of NCC patients with and without HA. The cross-sectional design precludes assessment of the direction of the relationship between seizures, EEG abnormalities and HA in patients with NCC. Nevertheless, previous studies strongly suggest that this relationship is most likely bidirectional, irrespective of pathogenetic mechanisms involved [28, 36]. While the lack of volumetric assessment of hippocampi may be a potential weakness, the Scheltens' medial temporal atrophy scale has proved reliable for grading HA when compared to volumetric measurements [43]. Immunological tests for detection of anticysticercal antibodies or cysticercal antigens were not performed because results of such tests are erratic in patients with calcified cysticerci, and could lead to misinterpretation [44]. Another limitation of the study, inherent to the EEG itself, is that a one-hour scalp EEG recording may miss subclinical epileptiform activity [33, 34]. Also, we cannot exclude that some patients, currently free of seizures or EEG abnormalities, will develop them in the future. On the other hand, strengths of this study include a population-based design with unbiased enrollment of participants, a high coverage of individuals with NCC diagnosis, and the systematic and uniform approaches followed for NCC diagnosis, MRI assessment of HA, and EEG abnormalities.

In conclusion, this study confirms the high prevalence of HA among patients with NCC and suggests that multiple pathogenetic mechanisms may be involved in this association. While seizures and EEG abnormalities play a contributory role in the development of HA, it is likely that other mechanisms can lead to atrophy in these patients. Further studies are needed to identify biomarkers of inflammation in NCC patients to determine whether recurrent bouts of inflammation have an independent role in the development of HA. ■

Key points

- Calcified neurocysticercosis is associated with hippocampal atrophy, but pathogenesis of this association is still elusive.
- Recurrent seizures or periodic inflammation from distant foci of calcification are the most probable explanations for this association.
- This population study showed that seizures and EEG abnormalities play a minor contributory role in the development of hippocampal atrophy.
- Having a single calcification (as opposed to more than one) was inversely associated with hippocampal atrophy.
- It is possible that the burden of infection, leading to more inflammation, is involved in hippocampal atrophy development in these cases.

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Disclosures.
None of the authors have any conflict of interest to declare.

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