Neurocysticercotic Calcifications and Hippocampal Sclerosis: A Case-Control Study

Mateus de Oliveira Taveira, Marcia Elisabete Morita, Clarissa Lin Yasuda, Ana Carolina Coan, Rodrigo Secolin, Alberto Luiz Cunha da Costa, Fernando Cendes

School of Medical Sciences, University of Campinas-UNICAMP, Campinas, SP, Brazil, Department of Neurology, University of Campinas—UNICAMP, Campinas, SP, Brazil, Department of Medical Genetics, University of Campinas—UNICAMP, Campinas, SP, Brazil

☯ These authors contributed equally to this work.
* fcendes@unicamp.br

Abstract

Objective
The exact role of calcified neurocysticercotic lesions (CNLs) in epilepsy is yet unknown and controversial. Although the relationship between CNLs, epilepsy and mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) has already been addressed, to our knowledge, no study has actually provided strong statistical evidence, nor reported the ODDS ratio for these associations. Therefore, we designed this case-control study to assess the likelihood of having MTLE-HS versus other forms of epilepsy in the presence of CNLs.

Methods
In this case-control study we included 119 consecutive patients with epilepsy and 106 disease controls (headache) with previous CT scans. We subdivided cases into MTLE-HS and other epilepsies. We used brain CT scans to define presence or absence of CNLs. After exploratory analyses, we used logistic regression to analyze the association between CNLs, epilepsy subgroups and disease controls.

Results
CNLs were found in 31.09% of cases and in 11.32% of controls (p<0.001). The initial analysis comparing epilepsy versus controls revealed a significant association between CNLs and epilepsy (OR = 5.32; 95%CI = 2.43-11.54; p<0.001). However, when we compared MTLE-HS versus other epilepsies versus controls we confirmed that CNLs were associated with MTLE-HS (OR = 11.27, 95%CI = 4.73-26.85; p<0.001) but other epilepsies were not. We found no difference in the CNLs load and no difference in the location of the CNLs when we compared patients with MTLE-HS, other epilepsies and disease controls.

Significance
The inclusion of controls allowed us to estimate the likelihood of having epilepsy in the presence of CNLs. We found that patients with CNLs were 11 times more likely to have MTLE-
HS; however, the presence of CNLs did not change the odds of having other types of epilepsy. These findings raise the possibility of neurocysticercosis playing a role in the pathophysiology of MTLE-HS and need further confirmation in other series.

Introduction

Neurocysticercosis (NCC) infection is considered to be an important cause of epilepsy in developing countries [1, 2] and some studies suggest that up to a third of cases of epilepsy in endemic areas may be attributed to NCC [3–5]. Although the relationship between acute symptomatic seizures and NCC during its transitional stage has long been known [6], the exact role of calcified neurocysticercotic lesions (CNLs) in epilepsy pathogenesis (with or without hippocampal sclerosis (HS)) is yet unclear and controversial. Some studies suggest that there is a clear association between CNLs and epilepsy in general [2,7,8]. Others indicate that CNLs are not as inactive as previously thought, as indicated by perilesional edema, gliosis and contrast enhancement seen in MRI and perfusion MRI studies. [1,9]. However, a previous study showed that the presence of CNLs was not associate with the clinical and pathological findings nor with postsurgical outcomes in patients with HS; thus suggesting that CNLs could represent a coincidental pathology in the context of patients with HS and refractory seizures [10].

Mesial temporal lobe epilepsy (MTLE) is the most common form of epilepsy and HS is its most common pathological substrate [11, 12]. The association between MTLE with HS (MTLE-HS) and CNLs was also suggested by case reports and cross sectional analysis [2, 13, 14]. Some studies even suggest a causative role of CNLs in MTLE-HS [13, 15].

Although the relationship between CNLs, epilepsy and HS has been investigated by many authors [2, 9, 15], to our knowledge, none provided strong statistical evidence, nor reported the ODDS ratio for these associations. Given the controversy and lack of strong statistical evidences, we designed a case-control study to assess the likelihood of MTLE-HS in the presence of CNLs.

Materials and Methods

Ethics Statement

Our Research Ethics Committee (Comitê de Ética e Pesquisa- FCM/ Unicamp) approved the study. We were exempted from having to obtain written informed consent from subjects due to the retrospective nature of our study.

Participants

We conducted this case-control study at University of Campinas Hospital (HC-UNICAMP). We analyzed data from 268 consecutive cases (with confirmed diagnosis of epilepsy [16]) from our Epilepsy Clinics and 272 disease controls, who attended our Headache Clinics from July 2013 to September 2013 and excluded 315 that did not fulfill the study criteria (Recruitment details are displayed in Fig 1). We included patients who attended our Headache Clinics as “disease controls” (n = 106) and defined patients from our Epilepsy Clinics as “cases” (n = 119). Since we included consecutive individuals, we did not match cases and controls for gender and age. The rationale for choosing Headache Clinics patients as controls was the need to have subjects without epilepsy from the same population, with similar socioeconomic background and who had already been submitted to a brain computed tomography (CT) scan. In
addition, most of these patients had migraine or tension type headache, and even if the CNLs were somewhat related to the headache, they did not have epilepsy.

Inclusion criteria for both groups were having a brain CT scan and being older than 15 years old. The rationale for choosing this imaging method was because CT is superior to MRI scan to detect small calcified lesions [17]. However, all cases had also been submitted previously to a high resolution MRI with an epilepsy protocol for investigation of any underlying epileptogenic lesion in our Epilepsy Clinics.

Exclusion criteria for both groups were having progressive central nervous system (CNS) disease, CNS inflammatory disease, other diseases that may present with CNS calcifications such as neurotuberculosis and neurotoxoplasmosis, CT or MRI lesions characteristic of active NCC and patients with history of previously treated NCC. Patients with suspected CNS inflammatory disease at any point of their history, with inflammatory changes in the cerebral spinal fluid or other positive immunological tests, as well as those with CT or MRI suggesting any acute inflammatory lesions (i.e. contrast enhancement) were not included in this study. In the “case” group, we excluded the following subjects: one patient with neurotoxoplasmosis, one with Sturge-Weber Syndrome, three with tuberous sclerosis, four who were previously treated for NCC and three who had active NCC in the past. The rationale for excluding those patients was because we already know the relationship between acute symptomatic seizures and NCC during its transitional stage and by excluding patients with previous history of active NCC we aimed to minimize the influence of history of active NCC in our results (bias). From the “control group”, we excluded 13 patients who attended Headache Clinics and had also been diagnosed with epilepsy according to their medical records.

In summary, we included 119 cases and 106 controls with ages ranging from 16 to 84 years.
Data Collection and Classification

We collected the clinical data from each patient’s medical records. We then classified cases based on their electroclinical syndrome and epilepsy etiology (Table 1) following International League Against Epilepsy’s 2010 recommendation [18]. According to this classification, we were able to define an electroclinical syndrome based on semiological data, typical electroencephalography and MRI findings. Given our primary question was to evaluate the true relationship between CNLs and MTLE-HS, we further divided cases into 2 subgroups: patients with MTLE-HS (54 subjects) and patients with all other epilepsies (65 subjects). MTLE-HS was defined as patient with the diagnosis of temporal lobe epilepsy in the presence of signs of HS on MRI scans using an epilepsy protocol.

Brain CT Scan Analysis

We defined our primary variable of interest as the presence or absence of calcifications suggestive of NCC. We extracted information regarding the presence or absence of small parenchymal round calcifications from each radiological report. When radiological reports were not available, we assigned a qualified neurologist to evaluate the scans. According to Del Brutto’s diagnostic criteria for NCC [19], small parenchymal round calcifications are considered to be highly suggestive of NCC and constitute a major diagnostic criterion. Given that our patients also have one epidemiological criterion (NCC is endemic in Latin America) and one minor criterion (clinical manifestations suggestive of NCC such as seizures), we may classify them as probably having NCC. As CT scans were analyzed before this study, radiologists were “blinded” to our objectives and methods. The neurologist who evaluated the remaining CT scans was also blinded as to which group patients belonged.

If CNLs were present, we further classified patients according to number of CNLs (single or multiple), side of CNLs (left, right or bilateral) and location (in the temporal lobe, extratemporal and unknown). Patients with multiple calcifications were classified as located in the temporal lobe if at least one of the CNLs occurred in the temporal lobe, regardless the location of other calcifications; the unknown category was assigned if the exact location of all CNLs was not described in details on medical records (i.e. the scans were not available for review).

Table 1. Classification of cases according to electroclinical syndromes and epilepsy etiology based on ILAE’s latest recommendation [18].

| Electroclinical Syndromes                                      | Patients with epilepsy (n = 119) |
|---------------------------------------------------------------|----------------------------------|
| MTLE with hippocampal sclerosis (MTLE-HS)                     | 54                               |
| All other syndromes except MTLE-HS                            | 65                               |
| Unknown                                                       | 25                               |
| Stroke                                                        | 11                               |
| Tumor                                                        | 11                               |
| Malformation of cortical development                          | 9                                |
| Juvenile myoclonic epilepsy                                   | 4                                |
| Infection                                                     | 1                                |
| Gelastic seizures with hypothalamic hamartoma                 | 2                                |
| Epilepsy with GTCS alone                                      | 1                                |
| Trauma                                                        | 1                                |

*Abbreviations: ILAE = International League Against Epilepsy; MTLE-HS = mesial temporal lobe epilepsy with hippocampal sclerosis; GTCS = generalized tonic-clonic seizures.

doi:10.1371/journal.pone.0131180.t001
MTLE-HS and Presence of CNLs

Patients with both CNLs and MTLE-HS were also divided into subgroups according to the side of occurrence of CNLs in relation to the side of HS (bilateral, ipsilateral and contralateral).

Statistical Analysis

We performed data analysis using SAS System (Statistical Analysis System, version 9.2, SAS Institute Inc., Cary, NC, USA) for Windows. First, we ran an exploratory analysis, measuring frequencies for categorical data and descriptive statistics for quantitative data. We compared data between cases and controls using Mann-Whitney-U tests for numerical variables and chi-square tests for categorical variables. We subsequently performed both univariate (controls versus epilepsy) and multivariate (controls versus MTLE-HS versus other epilepsies) logistic regression analysis to investigate the relationship between CNLs and MTLE-HS and between CNLs and other epilepsies. Significance was defined as p<0.05 for all analysis.

Results

Baseline Information

From the original sample of 268 cases and 272 controls we ultimately included 119 cases (77 women, age = 44.49 ± 13.43 years; 95%CI) and 106 controls (78 women, age = 51.27 ± 15.46 years; 95%CI). The demographic distribution of cases and controls can be seen on Table 2. Controls were found to be significantly older (p<0.001) than cases when a Mann-Whitney-U test was performed; however, both groups were similar in terms of gender distribution (p = 0.15). Detailed information for each patient and disease-controls subjects can be found in the Supporting Information S1 Table.

Comparison between Epilepsy versus Controls

We identified CNLs in 31.09% of our cases. It is of notice that 11.32% of controls also had CNLs despite the absence of symptoms suggestive of acute phase of NCC in the past, such as seizures, on their medical history. This difference was significant (p<0.001). In general, CNLs were also more frequent in women than men (27.1% versus 10%; p = 0.004). When comparing all subjects with CNLs with all those without CNLs, there was no difference regarding their age (50.86 years ± 10.83 versus 46.8 years ± 15.62; p = 0.10).

Initially, we used a binary logistic regression to compare cases and controls using presence or absence of CNLs as the dependent variable adjusted for age and gender. We found that the presence of epilepsy was associated with CNLs (OR = 5.32; 95%CI = 2.43–11.54; p<0.001).

| Table 2. Demographics of cases and controls. |
|---------------------------------------------|
| Cases | Controls | p value |
|---|---|---|
| **Gender** | | p = 0.15 (Chi-square) |
| Male | 42 | 28 |
| Female | 77 | 78 |
| **Mean age (± SD)** | | p<0.001 (Mann-whitney) |
| 44.49 (±13.43) | 51.27 (±15.46) |
| **Calcification** | | p<0.001 (Chi-square) |
| 37 (31.09%) | 12 (11.32%) |

When comparing patients with MTLE-HS and other epilepsies, we observed no difference regarding their gender distribution (68.52% women on MTLE-HS versus 61.54%; p = 0.43), but found that patients with MTLE-HS were older (48.87 years ± 12.6 versus 40.85 years ± 13.1; p<0.001).

doi:10.1371/journal.pone.0131180.t002
meaning that the presence of calcification increases in 5 times the chance of having epilepsy in general.

**Sub-Analysis (MTLE-HS versus Other Epilepsies versus Controls)**

The sub-analysis aimed to compare patients with MTLE-HS (54 cases), controls (106 subjects) and patients with other epilepsies (65 cases). Using chi-square test on a 3x2 contingency table, we found that patients with MTLE-HS had a higher frequency of CNLs (28/54, 51.85%) when compared to both controls (12/106, 11.32%) and patients with other epilepsies (9/65, 13.85%) \( (p<0.001) \) as seen on Fig 2.

Subsequently, we performed a multinomial logistic regression using the same dependent variable (presence or absence of CNLs) with these 3 groups: MTLE-HS; other epilepsies and controls. After adjusting the analysis for age and gender, we observed that CNLs were associated with MTLE-HS compared to controls \( (OR = 11.27, 95\% CI = 4.73–26.85; \ p<0.001) \), CNLs were associated with MTLE-HS compared to other epilepsies \( (OR = 5.77, 95\% CI = 2.26–14.12; \ p<0.001) \) and that CNLs were not associated with other epilepsies as compared to controls \( (OR = 1.95, 95\% CI = 0.73–5.2; \ p = 0.18) \). For the association between CNLs and MTLE-HS the statistical power was higher than 90% (Table 3). These findings confirmed that neurocysticercotic calcifications were more frequent in patients who have MTLE-HS than in both controls.

![Fig 2. Total Number of Subjects with calcified neurocysticercotic lesions on CT scans.](https://doi.org/10.1371/journal.pone.0131180.g002)
and patients with other epilepsies; it also indicates that patients with CNLs were 11 times more likely to have MTLE-HS.

**Sub-Analysis (MTLE-HS versus Location of CNLs)**

In this sub-analysis, we included only cases and controls with CNLs and divided them in 3 groups: MTLE-HS (n = 28), other epilepsies (n = 9) and controls (n = 12). We analyzed whether there were any differences in location of CNLs (temporal, extratemporal, unknown) amongst those 3 groups. We did not find a significant difference (p = 0.58) in CNLs location between them as seen in Fig 3.

We did not find differences in CNLs load between these 3 groups (p = 0.14), as illustrated in Fig 4. The analysis of the CNLs side comparing to the side of HS showed that 21% of the CNLs were ipsilateral to the side HS, 17% were contralateral to the HS side and 62% had bilateral CNLs (including in this last group one patient that had bilateral HS).

**Discussion**

We found an association between neurocysticercotic calcifications and MTLE-HS. Our data showed that the association between CNLs and epilepsy in general is much influenced by patients with MTLE-HS (45.4% in our cohort); since the exclusion of MTLE-HS from the model/analysis yielded non-significant association between CNLs and other types of epilepsy.

The frequency of CNLs in our study is seemingly high (31% for cases overall, and 11% for disease controls). However, the frequency of CNLs in patients with epilepsy has been high in studies from the same region [2]. In addition, a recent study that invited 248 volunteers (age > 60 years) to perform CT or MRI scans also detected CNLs in 11% of these individuals (only 4 of these had epilepsy) [14].

Our findings are similar to that of Velasco et al [2], showing an association between CNLs and HS and suggesting that NCC is possibly a form of initial precipitating injury (IPI), rather than a major cause of epilepsy. The main difference between our study and that of Velasco et al [2] and others [14, 20, 21], is the inclusion of a disease control group, thus, providing stronger evidence for these associations, at least in the context of a hospital based population.

We also found a higher frequency of CNLs amongst women, as seen in previous studies [22, 23, 24]. The possible cause of this finding is still unknown.

We discuss here four possible explanations for our findings, as suggested previously in the literature [13, 15]. The first would be coincidence. The second possible explanation would be that NCC and MTLE-HS are associated, but are not causally related (e.g. due to a third unrelated factor, such as poor socioeconomic background). Third, NCC may be a direct cause of MTLE-HS or epilepsy. Fourth, the association between NCC and MTLE-HS is as part of the epileptogenic process (trigger) but not a direct causative factor.

The first theory claims that since both diseases are relatively common entities in endemic areas, they just happen to appear in the same patient as a coincidence. We do recognize that in some patients that might be the case, but we believe that this theory seems unable to explain the very high frequency of CNLs in patients with MTLE-HS found in our study (51.85%) or in

|                          | Odds ratio | 95% CI     | p value |
|--------------------------|------------|------------|---------|
| MTLE-HS versus controls  | 11.27      | 4.73–26.85 | <0.0001 |
| MTLE-HS versus other epilepsies | 5.77      | 2.26–14.71 | 0.0002  |
| Other epilepsies versus controls | 1.95      | 0.73–5.20  | 0.1806  |

doi:10.1371/journal.pone.0131180.t003
Fig 3. Location of neurocisticercotic calcifications in each group. This graph shows the percentage of subjects with calcifications located in the temporal lobe (Temporal), outside the temporal lobe (extratemporal) and unknown in each subgroup (MTLE-HS, other epilepsies, disease controls). There were no significant group differences considering the presence of calcifications in the temporal lobes. (p = 0.58) MTLE-HS = Mesial temporal lobe epilepsy with hippocampal sclerosis.

do:10.1371/journal.pone.0131180.g003

other studies: 17.7% and 37.2% in two studies of MTLE-HS patients submitted to surgery [10, 25] or 35.6% in a retrospective cohort [26].

The second theory does not deny a correlation between NCC and MTLE-HS, but it claims that there is no causative association between both: a third variable would be implicated in the pathophysiology of both. In statistics, correlation does not mean causation. In the case of NCC and MTLE-HS, for example, low economic status or genetic susceptibility to both conditions could lead to this association [15]. Although both groups (cases and controls) in our study had the same socioeconomic background, we cannot rule out the possibility of poverty or genetic susceptibility being the third variable to explain both NCC and MTLE-HS in our series.

The third theory states that MTLE-HS may be caused by direct inflammation and structural damage to the hippocampi or cortex by the acute phase of cysticerci located in the vicinity. This might be true for some specific cases, but probably does not explain all of them. For example, there are case reports of patients with a cysticercus in the hippocampus with MTLE-HS [27, 28]. Thus, we do not think this is the most important mechanism by which NCC could cause MTLE-HS, because in patients with MTLE-HS and NCC the calcified lesions are not necessarily located in the temporal lobes, as we demonstrated earlier in a different series of patients in our center [29]. In that study [29], like in the present study, we found no relationship
between localization of CNLs (temporal or extra-temporal) and seizure semiology (MTLE or other types of epilepsy).

The fourth theory suggests the presence of NCC could work as an IPI that would lead to HS, via multiple mechanisms, and then HS itself would cause chronic seizures, and frequently refractory epilepsy. There is evidence that some specific kinds of lesions or aggressions may cause mesial temporal lobe damage and as a consequence lead to HS, which would then cause MTLE [30, 31]. These aggressions are known as IPIs [31]. The most studied IPIs are prolonged febrile seizures, neonatal hypoxia, status epilepticus, trauma and meningoencephalitis [32]. This theory suggests that one plausible explanation for the association we have found is that NCC most likely represents one IPI in patients with predisposition to have seizures and therefore to develop MTLE-HS. Clinical or subclinical inflammation on the acute phase of infection would damage or aggravate a previously injured or predisposed hippocampus. The presence of inflammation is widely accepted [33] and a MRI perfusion study [1] suggests that even after resolution of the acute phase, with the formation of CNLs, there may still be inflammation induced by the acute phase. The CNLs would function both as a marker of previous damage to the hippocampus and as an active injury [34]. Another possible mechanism of epileptogenesis,
according to some authors, would be the degenerating cysts leading to the development of
electrical activity in the hippocampi through the phenomena of kindling, interictal discharge or
even subclinical seizures [13]. A previous study comparing patients with MTLE-HS with or
without CNLs found no difference in their post-surgical prognosis [10], which in our opinion
(although not directly proven by the present study) further supports the notion of NCC as an
IPI, given the presence of CNLs after surgery (even in the hemisphere contralateral to the surgical
resection) would not influence post-surgical outcome. This goes along with our finding that
NCC is more associated with HS, and hence MTLE-HS, than with other epilepsies in the con-
text of our series. Another circumstantial evidence that NCC may be an IPI for MTLE-HS is
the higher prevalence of MTLE-HS in developing countries, where NCC is endemic, compared
to developed countries [35, 36].

Limitations

There are some limitations to our study: our controls were not healthy volunteers, as it would
be unethical to submit healthy controls to unneeded radiation exposure. Therefore, it is possi-
ble that the frequency of CNLs differs between a healthy population and controls selected from
a Headache Clinics [37]. However, as discussed above, the rate of CNLs in our disease controls
was similar to that reported by Dell Bruto et al. [14].

Another limitation is that 43 out of 106 controls were using antiepileptic drugs, which raises
the possibility that some of them did not present with seizures simply because they were
already being treated.

Another limitation was that all patients with CNLs were considered to have NCC despite
not fulfilling criteria for definitive diagnosis. According to the most recent diagnostic criteria
[19], those patients would be considered to have a probable diagnosis of NCC based on the
findings of highly suggestive lesions on CT scan plus suggestive clinical manifestations and liv-
ing in endemic area. Additionally, our study is retrospective and uses data that had already
been described in medical charts or radiological reports. Another limitation is that not all con-
trols had undergone MRI scans, which might have shown HS even in asymptomatic (e.g. with-
out epilepsy) patients [38]. In addition, 45.8% of 119 cases had MTLE-HS probably due to a
referral bias, as our institution is a reference center in its region for the treatment of refractory
epilepsy. That said, it might not be feasible to prove or disprove the association between CNLs
and MTLE-HS in a population-based study, given the relatively low prevalence of the former
in the overall population.

In conclusion, our study showed a significant association between CNLs and MTLE-HS and
indirectly suggests that NCC may acts as an IPI in patients with predisposition to develop HS
or to have seizures. However, our data does not support the association between NCC and
other types of epilepsy. It is important to note that these findings cannot be extrapolated to the
general population, first, because it is a series from a tertiary center, and second, because of the
heterogeneity of the other subgroups in our study. In this article, we review several different
mechanisms by which NCC and MTLE-HS might be associated. We believe that the relation-
ship between NCC and MTLE-HS is complex and probably results from the combination of all
possible mechanisms discussed herein.

Given the controversy and lack of strong statistical evidences addressing the relationship
between CNLs, epilepsy and HS the results reported herein provide important statistical evi-
dence regarding the risk of epilepsy in the presence of CNLs. We found that the presence of
CNLs increases in 11 times the likelihood of having epilepsy with HS. This finding is important
for the understanding of the pathophysiology of NCC and HS and the concept of dual pathol-
ogy. The decision of considering the presence of CNLs in a patient with MTLE-HS as a possible
IPI, and not as a dual pathology, may have implications in treatment and prognosis for patients with CNLs and HS.

Statistical Analysis
Statistical analysis was conducted by Dr. Morita (Department of Neurology), Dr. Cendes (Department of Neurology) and Biostatistical Support Group from FCM—University of Campinas.

Supporting Information
S1 Table. Clinical and demographic data for all patients and disease-controls. (XLSX)

Acknowledgments
We would like to thank the Biostatistical Support Group from FCM – University of Campinas (technical help with logistic regression analysis).

Study supported by FAPESP, grants # 2013/07559-3 and 2013/21265-2.

Author Contributions
Conceived and designed the experiments: MOT MEM FC. Performed the experiments: MOT MEM. Analyzed the data: MOT MEM CLY ACC RS ALCC FC. Contributed reagents/materials/analysis tools: FC. Wrote the paper: MOT MEM CLY ACC RS ALCC FC.

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