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Seizure in people with newly diagnosed active or transitional neurocysticercosis

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ABSTRACT

Purpose: The aim of this study is to describe seizure as a presenting symptom in individuals with recently diagnosed neurocysticercosis (NCC).
Methods: Using logistic regression, we examined the probability of having seizures as a presenting symptom among those with active or transitional NCC by host age and gender, and by number of cysts, location of the cysts in the brain, and phase of evolution of the encysted parasite.
Results: We found that the odds of having seizures as presenting symptom for those in the youngest age group (3–24 years old) were 12.9 times that of the oldest participants (age 55–82 years) ($p = 0.006$). People with cysts in parenchymal locations had a significantly higher odds of seizures compared to those with all their cysts elsewhere (ventricles or subarachnoid) (OR = 6.2, $p = 0.028$); and the number of cysts was significantly associated with having seizures (OR = 1.1, $p = 0.026$). Host gender and cyst phase were not significantly associated with having seizures after adjusting for confounders and covariates.
Conclusion: Children, those with cysts in parenchymal locations, and those with a higher number of cysts appear to be more likely to experience seizure when they have NCC cysts in the active or transitional stage.

1. Introduction

Neurocysticercosis (NCC) is an infection of the central nervous system (CNS) with the larval stage of the intestinal pork tapeworm *Taenia solium* (*T. solium*). Humans become infected with the larval form of the parasite through the fecal–oral route by ingesting parasite eggs from a human harboring an adult tapeworm in the intestines.[1] While the larval form of the parasite can reside in almost any human tissue,[2] it has an affinity for nervous system tissue,[3,4] where it forms a cyst enclosing the parasite. The encysted parasite progresses through three distinct phases of evolution: (1) the active phase, in which the parasite is alive, (2) the transitional phase, in which the parasite has begun to degenerate and is being attacked by the host's immune system, and (3) the inactive phase, in which the parasite is deceased but has left a calcified nodule.[5]

NCC is possibly the most heterogeneous infection of the CNS, with a wide variety of clinical manifestations.[6–9] However, the most common symptom is seizure.[4,10–14] Reports suggest that seizures are the most frequent manifestation of cysts located in the brain parenchyma;[3,15–21] and seizures have been reported in patients with cysts in all three phases of evolution (active, transitional, and inactive).[4,12] Seizures associated with cysts in the transitional stage, characterized by edema surrounding the degenerating cyst, are considered to be provoked or acute symptomatic. Seizures associated with active or inactive cysts

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are considered to be unprovoked.[4,22] Inactive cysts may cause seizures through residual perilesional gliosis,[23] or scarring,[12] that results in a chronic epileptogenic foci.[4]

Generalized seizures and partial seizures with secondary generalization are the most common types experienced by people with NCC; and only a minority of those infected with NCC present with complex partial seizures.[4,12,14,15,23] It has been suggested that the low frequency of complex partial seizures in those with NCC is due to the high proportion of NCC patients with cysts in the parietal and frontal lobes and the relatively smaller proportion with temporal lobe cysts.[23] However, a thorough examination of seizure in NCC patients by the location and phase of the cysts has not been done.

The aim of this investigation is to examine seizures as a presenting symptom in people diagnosed with NCC in detail. We compared the probability having seizures as a presenting symptom among symptomatic NCC patients by host age and gender, by location of the cysts in the brain, and by phase of evolution of the parasite. We also describe seizure classification by patient age and gender and cyst location and phase.

2. Methods

2.1. Study design and subjects

The data described in this paper come from the baseline assessment of participants of a clinical trial of treatment for symptomatic NCC infection conducted in Ecuador between 2001 and 2003.[24] For this trial, individuals with newly diagnosed NCC were randomized to receive symptomatic treatment plus albendazole or symptomatic treatment plus placebo. NCC patients were eligible to participate in the study if they presented with new onset of symptoms associated with NCC within the past 2 months and had active and/or transitional NCC cysts apparent on CT or MRI. Patients with only inactive NCC cysts were not eligible to participate in the study. In addition, those who were pregnant, had active tuberculosis, syphilis, papilledema, ocular cysticercosis, active ulcers, or some other progressive and life threatening disorder were also considered ineligible. Partway through the study we also excluded patients with ventricular shunt for safety reasons due to the poor outcome of shunted NCC patients. Finally, patients who had received treatment for NCC during the past year or who had undergone systemic treatment with steroids within 30 days of presentation were ineligible for this study.

2.2. Data collection

At enrollment into the study, we collected basic demographic information, including participant's age and gender, as well as information about all health problems experienced during the 2 months prior to study enrollment through the reading of a symptom checklist. Patients who reported having had seizures during this time period were then asked to describe each seizure. Based on the patient's description, the seizures were classified according to the International League Against Epilepsy categories: Partial not specified, simple partial, complex partial, partial with secondary generalization, and generalized.[25]

A CT or MRI taken no more than 2 weeks prior to study enrollment was read by two neuroradiologists, one in Ecuador and one in the United States (US). The cysts were categorized according to location within the brain and phase of evolution as defined by Carpio et al.[5] Cyst phase was classified as active, transitional, or inactive. Although patients with only inactive cysts were ineligible for this study, many of the patients with active or transitional cysts also had inactive cysts. In addition, racemous cysts, or clusters, which can include cysts in both the active and transitional phase, were enumerated and analyzed as a separate group. The inter-rater reliability of the scan readings was acceptable, with kappas ranging from 0.4 to 0.7 for identifying that a patient had cysts in a specific location or phase of evolution. The readings of the US radiologist are used in these analyses.

A written informed consent form for study participation was signed by all participants or, in the case of participants under 18 years old, by their legal guardian. Participants under 18 years old also provided oral assent for participation. Approval for the study was granted by the Columbia University Institutional Review Board, the Office for Protection from Research Risks (OPRR) of National Institutes of Health, as well as the Ethics Committees at the participating hospitals in Ecuador.

2.3. Statistical analysis

Data were processed and statistics generated using SPSS 16.0 (Chicago, Illinois). We examined seizure status by characteristics of the patient and of the infection (host age and gender, cyst location and phase). We categorized patients according to the presence of NCC cysts in the specified location (parenchymal, subarachnoid, and intraventricular) and phase group (active, transitional, inactive, and cluster). All clusters, whether in the active or transitional phase, were included only in the cluster category. The location and phase categories were examined in two ways, first as an indicator for the presence of any cysts in the specified location or phase, in which patients could have cysts in more than one category of phase or location (i.e. the categories were not mutually exclusive). We also constructed categorical variables for location and phase comparing those with only cysts in the specified location or phase to those without such cysts (mutually exclusive categories). Because we excluded patients who had only calcified cysts from the clinical trial, we are not able to examine the association of having only calcified cysts with seizure. For the analyses regarding seizure classification, we used the description of the seizure that occurred closest to the time of the interview in order to reduce misclassification due to recall errors.

We used the Pearson chi-squared statistic to assess statistical significance when examining the frequency of categorical variables. When one or more cell in a table had an expected count of less than 5, the Fisher's exact test was used for assessing statistical significance. The number of seizures, which is not normally distributed, was examined using nonparametric methods, specifically the Mann–Whitney *U* or Kruskal–Wallis tests.

Logistic regression models were run to assess the association of having seizures as a presenting symptom with patient age and gender and with cyst location (parenchymal, subarachnoid and intraventricular) and phase (active, transitional, cluster and inactive) while controlling for covariates and potential confounders. Again, we modeled cyst location and phase in two ways. First we ran the model with the non-mutually exclusive indicators for having any cysts in the specific location of phase. Second we created mutually exclusive dummy variables for cyst location (only parenchymal cysts, only extraparenchymal cysts, both parenchymal and extraparenchymal cysts) and phase (only active cysts, only transitional cysts, only clusters, cyst in more than one phase). There were too few participants with only subarachnoid cysts and only intraventricular cysts to examine these locations separately and therefore the two locations were combined into a dummy variable for having only extraparenchymal cysts. In addition, as mentioned above, we have no study participants with only calcified cysts and therefore those participants are included in the group with cysts in more than one phase. The reference category used for cyst location was extraparenchymal cysts, and the reference category for cyst phase was active cysts.

We also examined three indicators for economic and physical barriers to healthcare access as potential confounders, as they may

influence whether or not a patient will seek care for symptoms less severe than seizures. Specifically, we looked at: patient's monthly household income, which may determine the ability to pay for, and therefore receive care; the distance of patient's residence from a paved road, and location of the patient's residence in the same province as the treating hospital, both of which may influence physical access to a tertiary care hospital with facilities for diagnosing and treating NCC. We also adjusted for type of image (CT or MRI) because transitional cysts are easier to identify in MRI than CT.[26] Therefore measurement error rates will differ depending on which type of image is being read. In addition, we examined the total number of cysts, and therefore the regression analyses excluded patients with too many cysts to count, which was determined to be more than 49 cysts by our neuroradiologists.

3. Results

3.1. Description of sample and distribution of seizures (Table 1)

A total of 172 neurocysticercosis patients enrolled in the study, 56% of whom were male. The age range was 3–82 years. Half of the participants had a CT scan ($n = 86$) and half an MRI ($n = 86$) taken, from which NCC was diagnosed and details about the cysts were collected. A total of 107 patients reported having new onset of seizures within 2 months of enrollment. There was no significant difference in the type of image taken (CT versus MRI) by seizure status (54.7% of those with seizures and 45.3% of those without seizures had a CT scan, chi-square $p = 0.068$). Those who had seizures had had an average of 3.4 seizures in the previous 2 months.

There was no difference in the proportion of men and women having seizures ($p = 0.819$), and among those who had seizures there was no gender difference in the number of seizures experienced in the past 2 months ($p = 0.479$). The age groups were similar in terms of the proportion experiencing seizures, with the exception of patients age 3–19 years old, of whom all (100%) had seizures ($p = 0.004$). Among those who had seizures, there was no significant age-difference in the number of seizures experienced in the past 2 months ($p = 0.819$).

We had a baseline scan on 170 patients. Patients with transitional cysts were significantly more likely to have seizures compared to patients with no transitional cysts (69.6% versus 50.0%, $p = 0.010$), and among those who had seizures, those with transitional cysts had significantly more seizures in the past 2 months ($p = 0.032$). Patients with clusters (all of which were extra-axial) were significantly less likely to have seizures (31.0% versus 68.1%, $p = 0.000$). There was no significant difference in the probability of having seizures or, among those who had seizures, in the number of seizures experienced in the previous 2 months, among those with active cysts compared to those without such cysts. The presence of inactive cysts was also not associated with the probability of having seizures or with the number of seizures experienced.

Patients with parenchymal cysts were significantly more likely to have seizures compared to patients without parenchymal cysts (67.8% versus 26.1%, $p = 0.000$). Patients with cysts in the parietal lobe (69.3 versus 50.7, $p = 0.014$) or occipital lobe (72.1% versus 56.0%, $p = 0.037$) were also more likely to have seizures compared to patients without any cysts in that location. Patients with subarachnoid cysts were significantly less likely to have seizures compared to patients without subarachnoid cysts (42.3% versus 75.8%, $p = 0.000$). Among those who had seizures, there was no significant difference in the number of seizures experienced by cyst location.

Limiting the comparisons to patients with only cysts in the specified location or phase compared to those without cysts in that location or phase did not change the results, except that the increased probability of reporting seizures by patients with cysts in the frontal lobe became statistically significant (92.3% versus 53.5%, $p = 0.009$), and the association of seizures with cysts in the occipital lobe was no longer statistically significant (80.0% versus 56.0%, $p = 0.389$), probably due to the small number of patients with only occipital lobe cysts ($n = 5$).

We further examined the patients under age 20 years in an attempt to determine if one possible explanation for the high proportion (100%) of that group experiencing seizure was that they had new onset idiopathic epilepsy (presumed genetic) with the NCC cysts being discovered coincidentally when the seizure cause was investigated. Of the 19 patients age 0–19 years for whom we had scan data, 15 (78.9%) had only transitional cysts, while 4 had only active cysts; 18 of the 19 patients had parenchymal cysts and one had both intraventricular and subarachnoid cysts. The majority of these patients had only 1 cyst ($n = 15$), while one patient had 4 cysts, one had 33 cysts and two patients had too many cysts to count (>49). Looking at the 6 patients under 11 years old, 5 had only 1 transitional cyst, while 1 had more than 50 active cysts and all the cysts in this group were parenchymal cysts. Thus the majority of the patients in the youngest age group have provoked seizures (associated with transitional cysts) and parenchymal cysts.

3.2. Logistic regression models (Table 2)

Because all patients under age 20 years had seizures, we expanded the youngest age group to patients age 3–24 for the regression models, and then adjusted the other age groups into approximate 10-year intervals to maintain a sufficient number within each category. In the adjusted logistic regression model controlling for having any cysts in each location and phase (non-mutually exclusive indicators) as well as measures of healthcare access, type of image (CT or MRI), and number of NCC cysts, patients under age 25 years had an odds of seizure that was 12.6 times that of patients over age 55 years ($p = 0.007$). There were no other significant differences in the odds of having seizures by age group, nor was there any significant gender difference.

In that same adjusted logistic regression model, there was no significant association between seizure and having any cysts in a specific phase. However, patients with cysts in the brain parenchyma had an odds of seizures that was 6.1 times higher than that of patients without parenchymal cysts ($p = 0.030$), while patients with subarachnoid cysts had a significantly lower odds of seizure compared to patients without subarachnoid cysts (OR = 0.3, $p = 0.020$). The total number of cysts was also significantly associated with the odds of having seizure such that for each additional NCC cyst, the odds of seizures increased by 10% ($p = 0.028$).

When the cysts were examined as mutually exclusive categories for phase (only active cysts, only transitional cysts, only clusters, or cysts in more than one phase) and location (only parenchymal cysts, only extraparenchymal cysts, or cysts in both parenchymal and extraparenchymal regions), the conclusions were the same. Those aged 3–24 years had a significantly higher odds of having seizure compared to those aged 55–82 years (OR = 7.5, $p = 0.018$), those with only parenchymal cysts had a higher odds of seizure than those with only extraparenchymal cysts (OR = 3.9, $p = 0.005$), and total number of cysts was positively associated with seizure (OR = 1.1, $p = 0.015$).

3.3. Seizure classification (Table 3)

Of the 107 patients who reported seizures at baseline, 44 had had only one seizure. Of the 63 patients who had had more than

Table 1
Seizures by gender and age of patient and phase and location of cysts.

Variable	Total number (%)	Number (%) with seizures	*p*-value for Pearson chi-square test	Mean number of seizures (SD) among those who had seizures	*p*-value for non-parametric test
Patient demographic characteristics					
Total	172 (100)	107 (62.2)		3.4 (4.2)	
Gender			0.819		0.479[a]
Male	96 (55.8)	59 (61.5)		2.9 (3.2)	
Female	76 (44.2)	48 (63.2)		4.0 (5.2)	
Age (years)			0.004		0.819[b]
3–19	20 (11.6)	20 (100)		3.7 (5.7)	
20–29	32 (18.6)	20 (62.5)		3.2 (4.3)	
30–39	34 (19.8)	20 (58.8)		3.4 (3.1)	
40–49	42 (24.4)	25 (59.5)		3.5 (4.0)	
50–82	44 (25.6)	22 (50.0)		3.1 (4.3)	
NCC cyst phase and location: presence of one or more cysts in specified phase or location					
Cyst phase					
Presence of active cysts	102 (60.0)	59 (57.8)	0.198	2.9 (3.7)	0.105[a]
No active cysts	68 (40.0)	46 (67.6)		4.1 (4.9)	
Presence of transitional cysts	102 (60.0)	71 (69.6)	0.010	3.8 (4.6)	0.032[a]
No Transitional cysts	68 (40.0)	34 (50.0)		2.6 (3.5)	
Presence of clusters	29 (17.1)	9 (31.0)	0.000	3.0 (1.2)	0.194[a]
No clusters	141 (82.9)	96 (68.1)		3.5 (4.5)	
Presence of inactive/calcifications	70 (41.2)	45 (64.3)	0.571	3.3 (4.7)	0.309[a]
No inactive/calcifications	100 (58.8)	60 (60.0)		3.5 (3.9)	
NCC cyst phase and location: presence of one or more cysts in specified phase or location					
Cyst location					
Presence of subarachnoid cysts	71 (41.8)	30 (42.3)	0.000	3.2 (3.5)	0.344[a]
No subarachnoid cysts	99 (58.2)	75 (75.8)		3.5 (4.6)	
Presence of intraventricular cysts	17 (10.0)	7 (41.2)	0.066	1.7 (1.1)	0.197[a]
No intraventricular cysts	153 (90.0)	98 (64.1)		3.6 (4.4)	
Presence of parenchymal cysts	147 (86.5)	99 (67.3)	0.000	3.5 (4.4)	0.499[a]
No parenchymal cysts	23 (13.5)	6 (26.1)		1.8 (0.8)	
Presence of frontal lobe cysts	99 (58.2)	67 (67.7)	0.061	3.3 (4.1)	0.576[a]
No frontal lobe cysts	71 (41.8)	38 (53.5)		3.7 (4.6)	
Presence of temporal lobe cysts	88 (51.8)	52 (59.1)	0.457	2.9 (3.4)	0.328[a]
No temporal lobe cysts	82 (48.2)	53 (64.6)		3.9 (5.0)	
Presence of parietal lobe cysts	101 (59.4)	70 (69.3)	0.014	3.6 (4.6)	0.815[a]
No parietal lobe cysts	69 (40.6)	35 (50.7)		3.1 (3.6)	
Presence of occipital lobe cysts	61 (35.9)	44 (72.1)	0.037	3.8 (4.8)	0.443[a]
No occipital lobe cysts	109 (64.1)	61 (56.0)		3.2 (3.9)	
Presence of basal ganglia and internal capsule cysts	52 (39.6)	34 (65.4)	0.519	2.7 (3.4)	0.330[a]
No basal ganglia and internal capsule cysts	118 (69.4)	71 (60.2)		3.8 (4.6)	
NCC cyst phase and location: presence of cysts only in specified phase or location					
Cysts phase					
Only active cysts	28 (29.2)	13 (46.4)	0.052	2.5	0.283[a]
No active cysts	68 (70.8)	46 (67.6)		4.1	
Only transitional cysts	45 (39.8)	37 (82.2)	0.001	4.1	0.042[a]
No transitional cysts	68 (60.2)	34 (50.0)		2.6	
NCC cyst phase and location: presence of cysts only in specified phase or location					
Cysts phase					
Only clusters	10 (6.6)	2 (10.0)	0.004[c]	2.5	0.656[a]
No clusters	141 (93.4)	96 (68.1)		3.5	
Cyst location					
Only subarachnoid cysts	17 (14.7)	2 (11.8)	0.000	2.5	0.579[a]
No subarachnoid cysts	99 (85.3)	75 (75.8)		3.5	
Only intraventricular cysts	2 (1.3)	1 (50.0)	1.000[c]	1.0	0.283[a]
No intraventricular cysts	153 (98.7)	98 (64.1)		3.6	
Only parenchymal cysts	91 (79.8)	69 (75.8)	0.000	3.7	0.602[a]
No parenchymal cysts	23 (20.2)	6 (26.1)		1.8	
Only frontal lobe cysts	13 (15.5)	12 (92.3)	0.009	2.9	0.842[a]
No frontal lobe cysts	71 (84.5)	38 (53.5)		3.7	
Only temporal lobe cysts	9 (9.9)	5 (55.6)	0.718[c]	2.2	0.330[a]
No temporal lobe cysts	82 (90.1)	53 (64.6)		3.9	
Only parietal lobe cysts	11 (13.8)	10 (90.9)	0.019[c]	4.7	0.311[a]
No parietal lobe cysts	69 (86.2)	35 (50.7)		3.1	
Only occipital lobe cysts	5 (4.4)	4 (80.0)	0.389[c]	6.5	0.475[a]
No occipital lobe cysts	109 (95.6)	61 (56.0)		0.5	
Only basal ganglia and internal capsule cysts	2 (1.7)	1 (50.0)	1.000[c]	2.0	0.920[a]
No basal ganglia and internal capsule cysts	118 (98.3)	71 (60.0)		3.8	

[a] Mann–Whitney test.
[b] Kruskal–Wallis test.
[c] Fisher's exact test.

Table 2
Adjusted logistic regression models looking at patient's gender, age, and presence of any cysts in the specified phase and location as predictors of seizure.

Variable	OR	95% confidence interval	*p*-value for crude model
Defining cyst phase and location as non-mutually exclusive indicators for the presence of any cysts in the specified phase or location ($n = 153$)[a]			
Gender[b]	1.4	0.6–3.4	0.464
Age 3–24[c]	12.6	2.0–78.6	0.007
Age 25–34[c]	2.2	0.6–7.9	0.216
Age 35–44[c]	1.2	0.4–3.8	0.776
Age 45–54[c]	2.8	0.8–9.9	0.111
Presence of active cysts	0.4	0.1–1.3	0.123
Presence of transitional cysts	1.4	0.5–4.1	0.556
Presence of clusters	1.0	0.3–3.7	0.966
Presence of calcified cysts	0.8	0.3–2.4	0.684
Presence of parenchymal cysts	6.1	1.2–31.2	0.030
Presence of subarachnoid cysts	0.3	0.1–0.8	0.020
Presence of intraventricular cysts	0.5	0.1–2.1	0.334
Total number of cysts	1.1	1.0–1.2	0.028
Income < $70 per month	1.3	0.5–3.2	0.590
Distance of residence from paved road (km)	1.0	0.9–1.0	0.230
Residence in same province as treating hospital	0.5	0.2–1.4	0.191
Type of scan (CT or MRI)[d]	1.2	0.4–3.6	0.695
Defining cyst phase and location as mutually exclusive dummy variables indicating having only cysts in the specified phase or location ($n = 153$)[a]			
Gender[b]	1.3	0.6–3.1	0.529
Age 3–24[c]	7.5	1.4–39.4	0.018
Age 25–34[c]	2.0	0.6–6.6	0.285
Age 35–44[c]	1.1	0.4–3.4	0.860
Age 45–54[c]	2.1	0.6–7.0	0.242
Only active cysts (reference)	–	–	–
Only transitional cysts	3.7	0.9–14.8	0.065
Only clusters	0.5	0.1–3.9	0.541
Cysts in multiple phases	1.0	0.3–3.4	0.964
Only parenchymal cysts	3.9	1.5–9.9	0.005
Only extraparenchymal cysts (reference)	–	–	–
Cysts in both parenchymal and extraparenchymal locations	4.5	0.3–67.5	0.273
Total number of cysts	1.1	1.0–1.2	0.015
Income < $70 per month	1.2	0.5–2.7	0.737
Distance of residence from paved road (km)	1.0	1.0–1.0	0.991
Residence in same province as treating hospital	0.6	0.2–1.5	0.257
Type of scan (CT or MRI)[d]	1.4	0.6–3.5	0.447

[a] Adjusted model excludes those with too many cysts to count.
[b] Reference group is male.
[c] Reference group is patients 55–82 years old.
[d] Reference group is CT scan.

one seizure, the classification of all the seizures experienced by an individual patient was the same for 45 patients, while 18 patients reported multiple seizures that, based on the patients' description, fit into differing ILAE classifications. The majority of patients with seizures experienced partial seizures with secondary generalization (41.1%), followed by generalized seizures (37.4%), simple partial seizures (13.1%), non-specified partial seizures (4.7%), and finally complex partial seizures (3.7%).

Men and women differed significantly in terms of the distribution of seizure classification ($p = 0.040$). Women had more partial seizures without generalization (non specified, simple, and complex) than men, while men had more partial seizures with secondary generalization and generalized seizures. In fact, all the complex partial seizures were reported by women. Upon limiting the comparison to generalized seizures and partial seizures with secondary generalization, the seizure types for which selection bias is less likely, the higher proportion of men within both classifications was not statistically significant ($p = 0.428$) (data not shown). There was no significant age difference in seizure classification ($p = 0.680$).

Looking at the 105 patients with seizures for whom we have a baseline scan, seizure classification differed significantly among patients with transitional cysts and parenchymal cysts, who were more likely to have partial seizures with secondary generalization ($p = 0.003$ and $p = 0.035$ respectively). None of the other cyst characteristics (location or phase) were significantly associated with the seizure classification. We had too few patients within each category of seizure type for multivariate regression modeling.

4. Discussion

We found that the proportion of patients with seizures in the youngest age category (3–19 years) was much higher, at 100%, compared with patients in all other age groups (between 50% and 63%). This association held in the regression model controlling for gender, location and phase of the cysts, total number of cysts as well as measures of healthcare access. Similar age differences among NCC patients have been previously reported.[27] While this higher proportion of patients with seizure in the youngest age group may be due, at least in part, to selection bias, as small children may be taken to the hospital for diagnosis and treatment only when they have obvious signs of illness such as seizures, in our study, half of the 20 patients in the youngest age category were between 15 and 19 years old. One might expect patients in this age range to be able to communicate less observable symptoms as well as adults over 20 years old. Meanwhile, most of the seizures in patients in the youngest age category appear to be provoked or acute symptomatic seizures due to transitional cysts in the brain parenchyma rather than new onset idiopathic epilepsy as most of the patients in this group had transitional parenchymal cysts. Thus it appears that children are more likely to have NCC-related seizures than adults. There seems to be a similar phenomenon in the traumatic brain injury literature. The probability of having acute symptomatic seizure following head trauma is much higher in children than in adults, even after controlling for severity of the trauma.[28–30]

Table 3
Number (percent) of patients with specified type of seizure by patient gender, age and phase and location of cysts.

	Number of patients with seizures who had cysts in specified location (% of total with seizures)	Partial not specified	Simple partial	Complex partial	Partial w/ secondary generalization	Generalized	*p*-value for Fisher's exact test
Total	107 (100)	5 (4.7)	14 (13.1)	4 (3.7)	44 (41.1)	40 (37.4)	
Patient characteristics							
Male	59 (55.1)	2 (3.4)	5 (8.5)	0 (0.0)	29 (49.2)	23 (39.0)	0.040
Female	48 (44.9)	3 (6.2)	9 (18.8)	4 (8.3)	15 (31.2)	17 (35.4)	
Age 3–19	20 (18.7)	2 (10.0)	1 (5.0)	1 (5.0)	10 (50.0)	6 (30.0)	0.680
Age 20–29	20 (18.7)	1 (5.0)	3 (15.0)	1 (5.0)	6 (30.0)	9 (45.0)	
Age 30–39	20 (18.7)	1 (5.0)	1 (5.0)	0 (0.0)	9 (45.0)	9 (45.0)	
Age 40–49	25 (23.4)	1 (4.0)	7 (28.0)	1 (4.0)	8 (32.0)	8 (32.0)	
Age 50–82	22 (20.6)	0 (0.0)	2 (9.1)	1 (4.5)	11 (50.0)	8 (36.4)	
Cyst phase							
Active	59 (56.2)	3 (5.1)	9 (15.3)	3 (5.1)	17 (28.8)	27 (45.8)	0.065
No active	46 (43.8)	2 (4.3)	5 (10.9)	1 (2.2)	26 (56.5)	12 (26.1)	
Transitional	71 (67.6)	3 (4.2)	8 (11.3)	0 (0.0)	36 (50.7)	24 (33.8)	0.003
No transitional	34 (32.4)	2 (5.9)	6 (17.6)	4 (11.8)	7 (20.6)	15 (44.1)	
Clusters	9 (8.6)	0 (0.0)	1 (11.1)	2 (22.2)	3 (33.3)	3 (33.3)	0.145
No clusters	96 (91.4)	5 (5.2)	13 (13.5)	2 (2.1)	40 (41.7)	36 (37.5)	
Calcifications	45 (42.9)	3 (6.7)	8 (17.8)	2 (4.4)	15 (33.3)	17 (37.8)	0.547
No calcifications	60 (57.1)	2 (3.3)	6 (10.0)	2 (3.3)	28 (46.7)	22 (36.7)	
Cyst location							
Subarachnoid	30 (28.6)	1 (3.3)	5 (16.7)	2 (6.7)	12 (40.0)	10 (33.3)	0.809
No subarachnoid	75 (71.4)	4 (5.3)	9 (12.0)	2 (2.7)	31 (41.3)	29 (38.7)	
Intraventricular	7 (6.7)	0 (0.0)	1 (14.3)	0 (0.0)	1 (14.3)	5 (71.4)	0.375
No intraventricular	98 (93.3)	5 (5.1)	13 (13.3)	4 (4.1)	42 (42.9)	34 (34.7)	
Parenchymal	99 (94.3)	5 (5.1)	13 (13.1)	2 (2.0)	42 (42.4)	38 (37.4)	0.035
No parenchymal	6 (5.7)	0 (0.0)	1 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	
Frontal lobe	67 (63.8)	3 (4.5)	9 (13.4)	0 (0.0)	29 (43.3)	26 (38.8)	0.123
No frontal lobe	38 (36.2)	2 (5.3)	5 (13.2)	4 (10.5)	14 (36.8)	13 (34.2)	
Temporal lobe	52 (49.5)	3 (5.8)	8 (15.4)	1 (1.9)	15 (28.8)	25 (48.1)	0.062
No temporal lobe	53 (50.5)	2 (3.8)	6 (11.3)	3 (5.7)	28 (52.8)	14 (26.4)	
Parietal lobe	70 (66.7)	4 (5.7)	11 (15.7)	1 (1.4)	28 (40.0)	26 (37.1)	0.401
No parietal lobe	35 (33.3)	1 (2.9)	3 (8.6)	3 (8.6)	15 (42.9)	13 (37.1)	
Occipital lobe	44 (41.9)	4 (9.1)	7 (15.9)	0 (0.0)	19 (43.2)	14 (31.8)	0.158
No occipital lobe	61 (58.1)	1 (1.6)	7 (11.5)	4 (6.6)	24 (39.3)	25 (41.0)	
Basal ganglia and I internal capsule	34 (32.4)	3 (8.8)	4 (11.8)	1 (2.9)	10 (29.4)	16 (47.1)	0.275
No basal ganglia and internal capsule	71 (67.6)	2 (2.8)	10 (14.1)	3 (4.2)	33 (46.5)	23 (32.4)	

While there was no gender difference in the proportion of patients having seizures, we did find a difference in the classification of seizure, with women reporting more partial seizures without secondary generalization and men reporting more generalized seizures and partial seizures with secondary generalization. This may represent a biological difference in NCC-related seizures, or it could be due to reporting or selection bias. The fact that there was no significant gender difference when limiting the analysis to seizures with generalization (partial seizures with secondary generalization and generalized seizures) may indicate that selection bias has played a role, with women seeking care more frequently for the less disruptive partial seizures without secondary generalization than men.

As with previous studies,[3,15,17–21] we found that patients with cysts in the brain parenchyma were more likely to have seizures, even after controlling for patient age, gender, cyst phase and total number of cysts. Patients with cysts in the parietal lobe and with cysts in the frontal lobe were also more likely to present with seizures compared to patients with cysts in other locations, although the association for frontal lobe cysts was only significant when limiting the comparison to those with only frontal lobe cysts verses those without. These associations are as would be expected from the literature.[23] However, the association of seizures with cysts in the occipital lobe has not been previously described in the literature and may warrant further study.

The literature describes seizures as being caused by cysts in all phases of evolution.[4,12] While we found transitional cysts to be associated with a significantly higher probability of seizure in the chi-square analysis (Table 1), in the regression models that adjusted for patient age and gender as well as the number and location of the cysts, no specific cyst phase was found to be significantly associated with having seizures (Table 2) and thus this lack of association after adjustment appears to be consistent with the literature.[4,12] However, anecdotal reports suggest that transitional cysts may be a more common cause of seizures than cysts in other phases. Our adjusted regression models do not support this. It is possible that the association of transitional cysts with seizure that some assume based on observation could be due, at least in part, to the fact that patients with transitional cysts are more likely to have cysts in the parenchymal region of the brain (95.1% of those with transitional cysts had parenchymal cysts versus 73.5% of those without transitional cysts, $p > 0.001$). Having parenchymal cysts was found in our models to be a strong (OR = 6.1) predictor of having seizures, independent of the phase of those cysts. In addition, people with NCC cysts in the transitional phase are reportedly more likely to experience symptoms in general compared to those with cysts in other phases.[31] Thus transitional cysts may be associated with all symptoms, not just seizures, and since all the patients in our sample were symptomatic, we would be unable find an association between transitional cysts and any specific symptom. Finally, we must note that in the adjusted logistic regression model, those with transitional did have a higher odds of seizures compared to those without transitional cysts (OR = 1.4 when looking at the odds of seizure among those with any transitional cysts versus those without and OR = 3.7 when comparing the odds of seizure in those with only transitional cysts versus those with only active cysts). It is possible that having transitional cysts is associated with some increased probability of seizure but we were underpowered to detect that difference. Additional studies with larger samples of NCC patients would be needed to assess whether patients with cysts in any

specific phase are truly more likely to experience seizures. However, it should be noted that some patients with only cysts in each phase (active, transitional, and clusters) experienced seizures, and therefore it seems that having cysts in any phase can cause seizures, not just cysts in the transitional phase.

The distribution of seizure type in our population was consistent with what is described in the literature,[4,12,14,15,23] with generalized seizures and partial seizures with secondary generalization being by far the most common type, and complex partial seizures occurring in only 4 patients. We found that half of our patients (52%) had at least one cyst in the temporal lobe and more than half of these patients (59%) had seizures (Table 1). Meanwhile, only one of the 4 patients with complex partial seizures had a cyst in the temporal lobe, while of the other 3 patients, one had cysts in the parietal lobe, one had cysts in the occipital lobe, and the last had cysts in the basal ganglia and internal capsule. Thus the hypothesis that the rarity of complex partial seizures is due to the low frequency of NCC cysts in the temporal lobe[23] is not supported by our data.

This study had a number of limitations that should be considered. First, some cysts might not be identified at baseline due to edema, and there might be some misclassification of location and phase of evolution for those cysts that were identified. While our inter-rater reliability was generally good, it was not perfect and thus some misclassification occurred in determining cyst phase and location. Another methodological challenge in our study is that seizures were classified based on patient description rather than observation. Therefore, our results might be influenced by reporting and/or recall bias. We might expect poor recall to cause partial seizures with secondary generalization to be misclassified as generalized seizures disproportionately as the initial partial seizure may not have been noticed or may be minimized during the reporting compared to the generalized portion of the seizure. In addition, we conducted a number of statistical tests, and therefore some of the associations we found could be due to chance. We also had small numbers within certain categories, and therefore we were under-powered for investigating some associations. For example, only 17 patients had intraventricular cysts, only 29 had clusters, and the number of patients by seizure classification gets very small (sample size range of 4–43). In addition, our youngest age category of 3–19 years included only 20 patients and as those patients were homogeneous in symptom, all having had seizures, we had to expand the age group to 3–24 years for the regression model in order to have sufficient variation in the outcome for effect estimation.

In this study we compared NCC patients who experienced seizures to those who experienced other symptoms in terms of patient and cyst characteristics. Larger sample sizes and improved sensitivity and specificity of CT and MRI scan readings might make the relationship between seizures and cyst characteristics clearer. Future research should work on reducing and quantifying misclassification of scan readings, perhaps by combining the readings of multiple neuroradiologists into a consensus reading. While we controlled for measures of healthcare access in the multivariate regression models, other biases, such as selection, reporting and recall bias, may have played a role in our study and should be minimized and evaluated in the future. Also replication of our findings is needed to rule out chance as an explanation. Despite these methodological challenges, we did find some associations that are a start toward identifying some of the factors involved in explaining NCC-associated seizures.

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