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Older Age in Subarachnoid Neurocysticercosis Reflects a Long Prepatent Period

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Abstract. Patients with subarachnoid neurocysticercosis (NCC) are usually older than those with parenchymal disease. Whether this difference reflects a prolonged presymptomatic period or a delay in diagnosis is not clear. From 408 eligible patients, we retrospectively compared the age at symptom onset in 140 patients diagnosed with parenchymal (pure viable or pure calcified) and subarachnoid NCC who had a confirmatory image available not more than 2 years after the beginning of symptoms. Patients with mixed (parenchymal and subarachnoid) NCC or those with parenchymal cysts at different stages (viable and/or degenerating and/or calcified) were not included. After controlling by sex and residence in rural endemic regions, the mean age at symptom onset in patients with subarachnoid disease was 13.69 years older than those with viable parenchymal disease. A long incubation period is a major contributing factor to older age at presentation in subarachnoid NCC, independent of delayed diagnosis or access to care.

INTRODUCTION

Neurocysticercosis (NCC) is the infection of the central nervous system by the larvae of the pork tapeworm *Taenia solium*, which carries significant neurologic morbidity in endemic areas.[1] Subarachnoid disease is the most severe form,[2] with a much higher mortality than parenchymal disease.[3] In all published series, patients with subarachnoid disease are older than those with parenchymal disease,[4–6] suggesting a long incubation period and/or a delayed diagnosis. The insidious nature of its symptoms and the low sensitivity of conventional neuroimages[7] can make the diagnosis of subarachnoid disease challenging. Although it has been theorized that subarachnoid disease may have a prolonged incubation period,[8] it is still not clear how much it contributes to the age differences seen in clinical settings. Moreover, no animal models of subarachnoid NCC exist to clarify this point.

Using available data from a large consecutive series of patients with diverse types of NCC seen in a referral center, we compared the age at symptom onset between parenchymal and subarachnoid disease after adjusting for factors that could distort this relationship.

MATERIALS AND METHODS

This transversal study included subjects who had been consecutively enrolled in an observational cohort of patients with suspected NCC attending the Instituto Nacional de Ciencias Neurológicas, a neurological reference hospital in Lima, Peru. Of a total of 885 enrolled participants, 171 did not have visible NCC lesions on available neuroimaging and 107 had no recorded information on when they started symptoms. Patients with intraventricular NCC ($N = 78$), granulomatous parenchymal NCC ($N = 20$), and mixed NCC (parenchymal and subarachnoid; $N = 79$) and those with parenchymal cysts at different stages (viable and/or degenerating and/or calcified; $N = 22$) were excluded, leaving an initial eligible population of 408 patients (Figure 1).

The age at symptom onset was defined as the age at which the patient presented one of the following symptoms: headache, seizures, and/or intracranial hypertension (ICH). According to neuroimaging (computed tomography [CT] or magnetic resonance imaging [MRI]), patients were categorized in the following groups: 1) viable parenchymal NCC: patients with only viable cysts inside the brain parenchyma; 2) calcified parenchymal NCC: patients with only intracranial calcifications on brain CT/MRI; or 3) subarachnoid NCC: patients with only viable NCC lesions in the subarachnoid space.

Clinical and laboratory findings were reviewed and assessed for the entire eligible population of 408 patients. The main analysis included only the subset of patients for whom a confirmatory image had been obtained not later than 2 years after symptom onset ($N = 140$) to reduce the likelihood of changes in the type of NCC between symptom onset and imaging and to minimize recall bias (overinterpretation of old mild, nonspecific symptoms as related to NCC). Additionally, a sensitivity analysis using all the data ($N = 408$) was conducted with different cutoff points between the onset of symptoms and available confirmatory neuroimaging to confirm our findings in the target subgroup.

Means, medians, and frequencies were reported for descriptive purposes. The age at symptom onset was compared between categories using the Kruskal–Wallis and Mann–Whitney tests. Categorical variables were compared using χ^2 tests. Mean differences between groups were obtained after controlling by sex and place of residence using a multivariable generalized linear model (identity link, Gaussian family) with a sandwich estimator of variance. All statistical analyses were performed using a standard software package (STATA, version 17.0; StataCorp, College Station, TX).

This study was approved by the institutional review board of the Universidad Peruana Cayetano Heredia, Lima, Peru. To protect the subjects' personal information, all personal identifiers were excluded from the study databases.

RESULTS

The characteristics of the 408 participants with either viable parenchymal NCC, calcified parenchymal NCC, or subarachnoid NCC ($N = 408$) are shown in Table 1. These were

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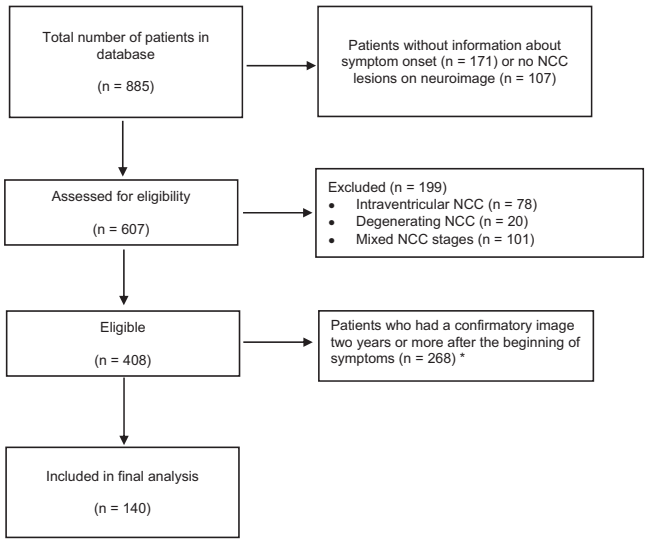

FIGURE 1. Study flowchart. NCC = neurocysticercosis. * Also evaluated as an additional sensitivity analysis.

178 male (43.6%), with a median age (IQR) of 43 years (33 (25th percentile)–57 (75th percentile)). Lima (a large metropolis) was the place of residence for 49.5% of the participants. Headache (84.6%) was the most frequently presented symptom, followed by seizures (65.7%) and ICH (19.1%). The median age and the median age at symptom onset were higher for those with subarachnoid NCC ($P < 0.001$). Headache, ICH, loss of consciousness, vomiting, dizziness, and focal motor deficit were associated with subarachnoid disease ($P = 0.001$, $P < 0.001$, $P = 0.004$, $P < 0.001$, $P = 0.027$, and $P = 0.011$, respectively). Seizures were associated with viable parenchymal disease ($P = 0.001$). Interestingly, patients with calcified parenchymal NCC reported more frequent (18.9%, $P < 0.001$) psychiatric symptoms. Furthermore, serologic assays showed that patients with subarachnoid NCC displayed higher values on a quantitative *T. solium* monoclonal antibody-based (Ag)-ELISA ($P < 0.001$) than both viable and calcified parenchymal NCC, and almost all reacted with three or more *T. solium* glycoproteins in the Enzyme-linked immuno-electrotransfer blot assay using lentil–lectin purified glycoprotein parasite antigens (LLGP-EITB) ($P < 0.001$), as previously described.[9,10]

TABLE 1
Demographic, clinical, and laboratory characteristics according to the type of neurocysticercosis ($N = 408$)

Characteristics	Types of neurocysticercosis*			
	Viable parenchymal NCC ($N = 59$)	Calcified parenchymal NCC ($N = 259$)	Subarachnoid NCC ($N = 90$)	P†
Sex, *n* (%)				
Female	27 (45.8)	151 (58.3)	52 (57.8)	0.206
Male	32 (54.2)	108 (41.7)	38 (42.2)	
Age (years)	31 (23–50)	45 (34–58)	47 (37–58)	< 0.001
Age at symptom onset (years)	28 (20–44)	35 (23–48)	41.5 (31–53)	< 0.001
Place of residence, *n* (%)				
Lima	32 (54.2)	132 (51.0)	38 (42.2)	0.265
Other	27 (45.8)	127 (49.0)	52 (57.8)	
Neuroimaging, *n* (%)				
CT	3 (5.1)	132 (51.0)	7 (7.8)	< 0.001
MRI	28 (47.5)	8 (3.1)	23 (25.6)	
Both	28 (47.5)	119 (46.0)	60 (66.7)	
Headache, *n* (%)				
Yes	43 (72.9)	217 (83.8)	85 (94.4)	0.001
Seizures, *n* (%)				
Yes	53 (89.8)	176 (68.0)	39 (43.3)	< 0.001
ICH, *n* (%)				
Yes	2 (3.4)	34 (13.1)	42 (46.7)	< 0.001
Loss of consciousness, *n* (%)				
Yes	9 (15.5)	29 (11.2)	23 (25.8)	0.004
Vomiting, *n* (%)				
Yes	8 (13.8)	43 (16.6)	38 (42.7)	< 0.001
Cognitive alterations, *n* (%)				
Yes	9 (15.5)	68 (26.3)	26 (29.2)	0.151
Dizziness, *n* (%)				
Yes	18 (31.0)	90 (34.9)	44 (49.4)	0.027
Focal motor deficit, *n* (%)				
Yes	3 (5.2)	27 (10.4)	18 (20.2)	0.011
Sensitive alterations, *n* (%)				
Yes	12 (20.7)	68 (26.3)	15 (16.9)	0.171
Psychiatric symptoms, *n* (%)				
Yes	4 (6.9)	49 (18.9)	4 (4.5)	0.001
Quantitative *Taenia solium* Ag-ELISA μg/mL	1.9 (0.7–8.1)	0.6 (0.5–0.8)	54.4 (33.8–62)	< 0.001
LLGP-EITB,‡ *n* (%)				
0	15 (25.4)	81 (31.3)	0 (0.0)	< 0.001
1 and 2	14 (23.7)	64 (24.7)	1 (1.1)	
3	14 (23.7)	81 (31.3)	14 (15.6)	
4–7	16 (27.1)	33 (12.7)	75 (83.3)	

Ag-ELISA = monoclonal antibody-based ELISA; CT = computed tomography; ICH = intracranial hypertension; LLGP-EITB = lentil–lectin glycoprotein enzyme-linked Immunoelectrotransfer blot; MRI = magnetic resonance imaging; NCC = neurocysticercosis.

* Frequencies for categorical variables and median with interquartile range for numerical ones.

† Kruskal–Wallis and χ^2 tests.

‡ Parasite glycoprotein antigens: GP50, GP42-39, GP24, GP21, GP18, GP14, and GP13.

The group selected for the final analysis of symptom onset included 140 patients with NCC (33 with viable parenchymal NCC, 62 with calcified parenchymal NCC, and 45 with subarachnoid NCC) who had a confirmatory image not later than 2 years after the onset of their symptoms. These were 72 males (51.4%), with an overall median age of 38.5 years (IQR: 28.5–54), and 77 (55%) resided in Lima. Bivariate analysis (Table 2) showed that an older age at symptom onset was associated with subarachnoid disease ($P < 0.001$) and residence outside of Lima (rural endemic areas) ($P = 0.024$).

After controlling by sex and place of residence, the mean age at symptom onset for patients with subarachnoid NCC was 13.69 years (95% CI: 6.57–20.81) and 4.78 years (95% CI: −0.72 to 10.29) older than that observed in patients with viable parenchymal NCC ($P < 0.001$) and pure calcified parenchymal NCC ($P = 0.089$), respectively. Likewise, the mean age at symptom onset for patients with calcified parenchymal NCC was 8.91 years (95% CI: 1.92–15.89) older than that observed in patients with viable parenchymal NCC ($P = 0.012$). Our results showed consistency across all cutoff points of years between symptom onset and neuroimage evaluation ($N = 408$; Supplemental Table 1).

DISCUSSION

In this series, patients with subarachnoid disease began symptoms much later than those with viable parenchymal disease, and this association persisted independent of the time between symptom onset and diagnosis of NCC. Although a long incubation period in subarachnoid NCC has been suggested by series reported previously, the design of this study compared the age at symptom onset in pure subtypes of NCC and adjusted by time to diagnosis (analyses not available in published series), thus allowing individual assessment of the contribution of the prepatent period by itself.

Previously, Fleury et al.[5] found a mean age at diagnosis of 39.1/38.9 years (male/female) for patients with subarachnoid disease ($N = 75$) and 32.3/32.2 (male/female) years for those with parenchymal disease ($N = 7$), and recently Marcin-Sierra et al.[4] also found an older age at diagnosis (44.2 versus 37.8 years) in subarachnoid NCC ($N = 114$) compared with parenchymal NCC ($N = 191$). Nevertheless, it was unclear whether this age difference at diagnosis already occurs at symptom onset.

Serpa et al.[11] compared the time to onset of symptoms since traveling for migrants from endemic areas as an attempt to quantify the incubation period and found a median of 2 years in parenchymal NCC ($N = 60$) and 11 years in extraparenchymal NCC ($N = 35$; only 13 subarachnoid). However, more than half of the cases included in this series were probable, not confirmed, NCC and there was no assessment of time between symptoms and diagnosis. Similarly, Nash and O'Connell[8] found a difference of 10 years between immigration from an endemic area and the development of symptoms in 34 patients with mixed subarachnoid NCC (only 17/34 were pure subarachnoid NCC), proposing an incubation period as long as 22.2 years using a methodology similar to that used by Dixon and Lipscomb.[12] Likewise, Del Brutto[13] published a systematic review of travelers to endemic areas who developed NCC upon returning to their home country and found an average of 2.2 years for patients with active parenchymal NCC ($N = 12$) and 20 years for extraparenchymal NCC ($N = 3$); the only patient with subarachnoid NCC started symptoms 34 years after travel. Note the small number of subarachnoid patients included in the same group with intraventricular NCC and mixed NCC, making it challenging to recognize which was the symptomatic lesion.

TABLE 2
Clinical and demographic characteristics associated with the age at symptom onset in patients with neurocysticercosis ($N = 140$)

Characteristics	*N* (%)	Age at symptom onset*	*P*†
Sex			
Female	68 (48.6)	45 (29–56)	0.121
Male	72 (51.4)	36 (24–52)	
Place of residence			
Lima	77 (55.5)	35 (24–49)	0.024
Other	63 (45.0)	43 (31–56)	
Type of neurocysticercosis			
Viable parenchymal NCC	33 (23.6)	24 (19–46)	< 0.001
Calcified parenchymal NCC	62 (44.3)	40.5 (31–53)	
Subarachnoid NCC	45 (32.1)	45 (33–59)	

NCC = neurocysticercosis.
* Median with interquartile range.
† Mann–Whitney or Kruskal–Wallis tests for nonnormally distributed variables.

Our study confirms these earlier findings and adds evidence that this prolonged time to diagnosis is not the product of delays in access to care or imaging. The relatively tolerant environment, the lower pressure and resistance, and the greater space for growth in the subarachnoid space are possible biological explanations for the prolonged prepatent period because the cyst might need more time to initiate symptoms as a result of mass effect or inflammation.[14,15] Age at enrollment was very similar for individuals with calcified NCC and those with subarachnoid NCC, although age at symptom onset was much higher for those with subarachnoid NCC (Table 1). This could result from recall bias if individuals with calcified NCC tend to recall symptoms earlier, or from a shorter period between symptom onset and enrollment, which could occur if symptoms due to subarachnoid NCC are severe enough to prompt searching for care. Place of residence was associated with the age at symptom onset (Table 2), which was older for patients from rural endemic areas. This finding might be related to differences in the age at parasite exposure and ingested parasitic load between these areas.

Our study has limitations. Selection bias due to unknown characteristics of patients who decided not to participate in the cohort study and recall bias owing to retrospectively obtained age at symptom onset might be present.

Finally, subarachnoid NCC characterization showed that these patients develop symptoms at an older age; present more frequently headache, ICH, loss of consciousness, vomiting, dizziness, and focal motor deficit; react to three or more glycoproteins in LLGP-EITB; and display a high quantitative *T. solium* Ag-ELISA value. These features should prompt the clinician to look for subarachnoid cysts by requesting appropriate neuroimaging.

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