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Cysticercosis and epilepsy in rural Tanzania: a community-based case–control and imaging study

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Abstract

Objective—To assess the contribution of neurocysticercosis (NCC) to the burden of epilepsy in a rural Tanzanian population.

Methods—We identified adult people with epilepsy (PWE) in a door-to-door study in an established demographic surveillance site. PWE and community controls were tested for antibodies to *Taenia solium,* the causative agent of NCC, and all PWE were offered a computed tomography (CT) head scan. Data on household occupancy and sanitation, pig-keeping and pork consumption were collected from PWE and controls and associations with epilepsy were assessed using chi-square or Fisher's exact tests.

Results—Six of 218 PWE had antibodies to *T. solium* (2.8%; 95% CI 0.6–4.9), compared to none of 174 controls (Fisher's exact test, $P = 0.04$). Lesions compatible with NCC were seen in

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eight of 200 CT scans (4.0%; 95% CI 1.3–6.7). A total of 176 PWE had both investigations of whom two had positive serology along with NCC-compatible lesions on CT (1.1%; 95% 0.3–4.0). No associations between epilepsy and any risk factors for NCC were identified.

Conclusions—Neurocysticercosis is present in this population but at a lower prevalence than elsewhere in Tanzania and sub-Saharan Africa. Insights from low-prevalence areas may inform public health interventions designed to reduce the burden of preventable epilepsy.

Keywords

cysticercosis; epilepsy; neuroimaging; Tanzania; serology; sub-Saharan Africa

Introduction

Taenia solium, the causative agent of human cysticercosis, is the commonest helminthic infection of the central nervous system worldwide [1] and is recognised as a leading cause of adult-onset epilepsy in endemic areas. Globally, up to 50 million people may be affected by cysticercosis [2] and up to 30% of all epilepsy may be associated with neurocysticercosis (NCC) [3]. *Taenia solium* carriage in human populations is perpetuated by two main factors: a pig population that is frequently exposed to human faecal matter (usually through free-range pig-keeping), and insufficient food hygiene at the meat inspection and/or food preparation stages that leads to consumption of undercooked encysted pork. When such circumstances prevail, the additional risk of human cysticercosis arises through faecal–oral exposure to *Taenia* eggs in environments where sanitation is poor [4]. Following ingestion of *Taenia* eggs extraintestinal tissues may become infected with the encysted larval stage and involvement of parenchymal brain tissue (i.e. neurocysticercosis) may lead to epilepsy [5].

The diagnosis of NCC can be difficult, with non-specific clinical manifestations (seizures, headaches, focal neurological deficits) and imaging findings that are often abnormal but seldom pathognomonic [6–8]. Serological tests using enzyme-linked immunosorbent assays (ELISA) or enzyme-linked immunotransfer blot (EITB) are available. Although these have sensitivities of 70–90% in experimental conditions [9–11], they may be less sensitive in patients with single lesions [7, 12], or less specific in highly endemic regions where 10% or more of the general population may have antibodies to *T. solium*, reflecting prior exposure as well as active infection or disease [13, 14]. When seeking to diagnose NCC serology should therefore be correlated with imaging findings wherever possible. In recognition of these difficulties diagnostic criteria have been developed that incorporate imaging, serological, clinical and epidemiological factors to arrive at diagnoses characterised as either definitive or probable NCC [15].

While NCC is considered to be the leading preventable cause of epilepsy in low- and middle-income countries, population-level data from sub-Saharan Africa (SSA) are relatively few. A systematic review identified 13 studies from eight countries conducted between 1989 and 2009 [1], 11 of which were suitable for inclusion in a meta-analysis which estimated a common odds ratio for developing epilepsy when cysticercosis was present of between 2.7 and 4.3 [16]. Only two studies from SSA outside of South Africa, both from Tanzania, have presented both imaging and serological findings to investigate the

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burden of cysticercosis/NCC among people with epilepsy (PWE). In northern Tanzania 17.9% of 212 PWE originally identified in a community-based study of epilepsy [17] had radiological evidence of NCC [18] and anticysticercal antibodies were subsequently detected by EITB in 28.4% of a subset of 81 PWE from the same study [19]. In southern Tanzania a community-based cross-sectional sero-prevalence study of human *T. solium* infection found that 53.7% of 123 people reporting epileptic seizures had anticysticercal antibodies detected by ELISA [20]. In the same study 28 people reporting seizures who had positive cysticercal antigen ELISA went on to have CT brain scans, all of whom had radiological evidence of NCC.

The aim of our study was to investigate the contribution of NCC to the burden of active convulsive epilepsy (ACE) in an adult population of rural northern Tanzania in which this issue has not previously been investigated. Exposure to *T. solium* among PWE and controls was determined serologically and neuroimaging in PWE was used to look for radiological evidence of NCC.

Methods

Study setting

The Hai district lies on the slopes of Mount Kilimanjaro in north-east Tanzania, covering an area of approximately 1300 km^2. Agriculture, livestock keeping (including pig-keeping), dairy farming, commercial mining and cottage industries are the main economic activities [21]. Computed tomography (CT) is available locally at Kilimanjaro Christian Medical Centre (KCMC), a large referral hospital in the nearby town of Moshi. Hai was originally established as a demographic surveillance site (DSS) in Tanzania by the Adult Morbidity and Mortality Project, an epidemiological programme conducted in partnership between the Tanzanian Ministry for Health and Newcastle University, United Kingdom [22]. The Hai DSS is comprised of 59 villages with a total population of 161 119 following the most recent census conducted in 2009 [23].

Participants and study design

Adult PWE were identified following a door-to-door census of the Hai DSS population during which a previously validated screening questionnaire to detect possible cases of epilepsy was administered [23]. After confirmation of epilepsy diagnoses by the research doctor (EH) all PWE were offered CT imaging of the brain and asked for a blood sample to be tested for antibodies to *T. solium*. All seizures and epilepsies were classified according to currently accepted criteria [24].

For each PWE contributing a blood sample six age-, sex- and village-matched controls were identified by random number sequence from the census database used in the prevalence study. Individuals from each group of six were approached in turn until one agreed to participate in the study. All controls were also asked for a blood sample; demographic data on age, sex, ethnic group, religion, educational level, household occupancy, domestic sanitation, pork consumption and pig-keeping were collected from all PWE and controls.

Imaging and serology

CT scans were done at KCMC using a Philips Tomoscan 4000 single-slice spiral scanner. Pre- and post-contrast scans were performed with 10-mm-thick slices. All CT scans were reviewed locally by a consultant radiologist (AJ) to exclude any pathology requiring immediate further investigation or management and subsequently reviewed in the United Kingdom by two neuroradiologists (AI and DB). Blood samples were analysed at the KEMRI-Wellcome research laboratory in Kilifi, Kenya, for the presence of anticysticercal antibodies. A Western blot assay utilising recombinant *T. solium* antigens to detect antibodies to cysticercosis (rT24H antigen) and taeniasis (rES33 antigen) was used. This technique is 97.0% sensitive and 99.4% specific for detection of NCC with two or more cysts, and 99.4% sensitive and 93.9% specific for detection of taeniasis [25]. For comparison of serology results a sample size of 134 cases and controls (total sample 268) was required to detect an odds ratio of 4.6 with 80% power and 5% significance level, based on data derived from a community-based case–control study of cysticercosis and epilepsy performed in Burundi [26].

Diagnoses of NCC in our study were made based on a combination of clinical, serological and radiological findings, according to accepted diagnostic criteria [15]. We anticipated that cysticercosis would be present in the Hai DSS population, as elsewhere in Tanzania, due to a number of epidemiological factors. Firstly, the majority of adults identified in the prevalence study (71.5%) suffered from focal-onset seizures, suggesting a considerable burden of acquired or late-onset epilepsy [23]. Secondly, the 2009 census identified 2270 of 43 794 (5.2%) households that kept pigs. Smallholder livestock production such as that seen in Hai district is associated with poor animal husbandry practice [27] and although we found no contemporary data on porcine cysticercosis in the Kilimanjaro region, post-mortem examination of pigs in an abattoir in the nearby town of Moshi had previously demonstrated the presence of *T. solium* metacestodes in 6.9% of local pigs [28].

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 19. Categorical variables were compared using the chi-square test where all expected cell values were greater than five; Fisher’s exact test or the likelihood ratio were used for smaller expected cell numbers. Ninety-five per cent confidence intervals were calculated using the standard error of a proportion based on the binomial distribution. Non-normally distributed continuous variables were compared using the Mann–Whitney *U*-test. Comparisons between groups were restricted to those in whom serology was available.

Ethics

The ethics review committee of the Tanzanian National Institute of Medical Research approved the study. Informed consent was obtained from all PWE and controls participating in the study.

Results

Recruitment and blood sampling

Blood samples were obtained from 231 of the 291 PWE (79.4%) identified during the prevalence study. Of the 60 PWE without blood samples, 57 (95%) had either refused or were not available on blood sampling days and two (3.3%) had died since initial ascertainment. These individuals were similar to those in whom samples were available in terms of age (Mann–Whitney *U*-test = 6570.5, $z = -0.619$, $P = 0.54$) and sex ($\chi^2(1) = 0.091$, $P = 0.76$). We encountered a high refusal rate during recruitment, meaning that 1:1 and geographic matching were not achieved as intended. A total of 182 controls were finally included in the study, all of whom consented to give a blood sample, and 78.8% of 231 PWE who gave blood samples were matched to controls, these being drawn from 49 of the 54 villages (90.7%) in which PWE were identified. A total of 413 blood samples were collected, of which 21 (5.1%) were either damaged or insufficient and not suitable for analysis: 13 (5.6%) of 231 PWE and 8 (4.5%) of 182 controls ($\chi^2(1) = 0.32$, $P = 0.57$). A total of 392 samples were therefore analysed: 218 from PWE and 174 from controls (Figure 1). Among those with serology results available, PWE were younger than controls (median age 31 *vs.* 39 years, $U = 15833.0$, $z = -2.812$, $P = 0.005$), and fewer PWE than controls had completed primary education (52.9% *vs.* 77.5%; $\chi^2(1) = 24.621$ $P < 0.001$). Other demographic features were similarly distributed among the two groups (Table 1).

Serology results

Antibodies to *T. solium* were identified in 6 (2.8%) of 218 PWE and 0 (0%) of 174 controls. Of the six seropositive PWE three (50%) had antibodies to the T24 antigen only, one (16.7%) had antibodies to the ES33 antigen only and two (33.3%) had antibodies to both antigens. The overall seroprevalence of *T. solium* antibodies among PWE was 2.8% (95% CI 0.6–4.9) and there was weak evidence of an association between seropositivity and having epilepsy (Fisher's exact test, $P = 0.04$). Possible domestic and dietary risk factors for taeniasis and/or cysticercosis were compared between PWE and controls, with no significant associations being identified (Table 1).

Imaging results

CT head scans were available from 200 of 291 PWE (68.7%): 106 males (53.0%) and 94 females (47.0%). The proportions of males and females were similar between PWE who did and did not have a CT scan ($\chi^2(1) = 0.18$, $P = 0.89$), although PWE who did have scans were older than those who did not (median age 32 *vs.* 26 years; $U = 10\,466.5$, $z = 2.054$, $P = 0.04$). Lesions compatible with NCC were seen in 8 (4.0%) of 200 scans, with evidence of a greater frequency among females than males (7 (7.4%) of 94 females *vs.* 1 (0.9%) of 106 males; Fisher's exact test $P = 0.03$). There were no instances of viable cysts requiring antihelminthic treatment or of any other radiological findings warranting acute intervention. Radiological abnormalities were seen in 51 scans overall (25.5%), with the most frequent finding other than NCC being evidence of cerebrovascular disease, seen in 13 cases (6.5% of scans). Other findings included previous trauma, encephalomalacia, hydrocephalus, tumour and porencephalic cyst. These and other radiological findings have been published elsewhere [23]. CT scans were not obtained in 91 PWE due to refusal or unavailability of PWE to

travel to hospital for imaging (60 cases), the scanner not working on some study days (29 cases) or death since initial ascertainment (2 cases).

A total of 12 PWE had abnormal CT scans and/or positive serology; their demographic, clinical, radiological and serological characteristics are summarised in Table 2. All but one of these individuals had seizures that could be classified as focal in onset on clinical grounds alone, in advance of any investigation results. With regard to treatment, 10 (83.3%) stated they were using antiepileptic drugs (AEDs) at the time of initial assessment (seven using phenobarbitone, one using carbamazepine and two using phenobarbitone and phenytoin in combination), with only one reporting full control of their seizures on AEDs. All PWE identified in the study were either started on AEDs or given advice to optimise their therapy. The cohort remains under follow-up and it may be possible to examine the response to AED therapy of PWE with and without NCC in due course.

A total of 176 PWE underwent both investigations (CT and serology). Within this group six cases (3.4%) had lesions on CT compatible with NCC of whom two (33.3%) also had positive serology, giving a prevalence of definitive NCC among investigated PWE of 1.1% (95% CI 0.3–4.0).

Discussion

Neurocysticercosis is present in the Hai DSS with 4.0% of PWE having evidence of NCC on neuroimaging and 1.1% of fully investigated individuals having definitive NCC. The overall prevalence of individuals with anticysticercal antibodies, however, is markedly lower than in other areas of SSA where up to one-third of the general population may be seropositive, rising to nearly 60% among PWE [16, 29].

Within Tanzania two studies have identified higher proportions of individuals with positive serology and/or neuroimaging than those seen in Hai. In northern Tanzania Winkler *et al.* [30] found anticysticercal antibodies in 30% of 20 PWE who had NCC on CT scans and in none of 20 PWE without NCC (overall seroprevalence in PWE of 15%). No antibodies were detected in sera from 20 healthy controls. In an imaging study conducted in the same population, 17.9% of 212 PWE were found to have lesions either definitive for or compatible with NCC on CT scanning [18]. In the same study, 5.1% of 198 consecutive CT head scans performed for various clinical indications in people without epilepsy were also found to have evidence of NCC.

A more recent study of the prevalence and risk factors for *T. solium* infection conducted in the Southern Highlands of Tanzania found 45.3% of 830 individuals tested to be antibody-positive and 16.7% to be antigen-positive [20]. Contrast-enhanced CT scans were performed in 55 antigen-positive individuals, with 54.6% of these having evidence of NCC. Although this study was not designed to specifically examine the relationship between *T. solium* and epilepsy in this population, a history of seizures was obtained from 14.8% of the study population, with diagnoses of epilepsy being based on a questionnaire designed to collect information on human cysticercosis. The questionnaire was administered by a nurse, with no further discussion with a physician or neurologist, and the extraordinarily high prevalence of

epilepsy reported suggests that this screening method had a very low specificity. Furthermore, the authors describe partial seizures as being distinct from epileptic seizures, by which they perhaps mean to refer to generalised seizures, and report a higher prevalence still of 50.8%. Bearing these limitations in mind, antibody- and antigen-positivity among people considered to have epilepsy were 53.7% and 22.8% respectively, and all 28 people in this group with positive antigen serology were found to have NCC on CT scanning.

Authors from both of these studies comment on local animal husbandry practice and sanitary conditions, describing the presence of free-range pig-keeping, limited access to household sanitation and safe water and poor hand-washing practice.

In contrast to previous studies pointing to a higher burden of NCC in SSA than that seen in the Hai DSS, a comprehensive multisite study conducted across five countries (Ghana, Kenya, South Africa, Tanzania and Uganda) has recently reported on the prevalence of ACE and its risk factors [31, 32]. Among adults tested at two of the sites (Tanzania and Ghana), *T. solium* antibodies were found in 3.4% of 290 PWE and 1.9% of 421 controls (OR 1.98; 95% CI 0.72–5.43). Within the Tanzanian site (Ifakara), the seroprevalence rates among cases and controls were 2.9% and 0.3%, respectively (OR 15.42; 95% CI 1.84–129.10), the seropositive rate among PWE being similar to our findings from the Hai region. The same research group has also reported on the individual and combined association between multiple parasitic infections and ACE, based on serological markers [33]. A total of 986 PWE and 1313 controls were studied across the five sites, with exposure to *Onchocerca volvulus*, *Toxocara canis* and *Toxoplasma gondii* being associated with an increased prevalence of ACE. In the Hai DSS, the proportion of adult PWE with clinically apparent focalonset seizures was high at 71.5% [23]. The majority of these remain unexplained, with brain lesions visible on CT, including NCC, being seen in only 25.5% of scans and only a limited contribution from *T. solium* to the burden of epilepsy in this population having been demonstrated. Further investigation for other parasitic causes of acquired epilepsy in this population would therefore be of interest.

While NCC appears to be an important cause of epilepsy in parts of SSA, the picture is not uniform and detailed assessments of the socio-economic and environmental circumstances in which different communities live will be necessary to inform any public health interventions designed to tackle this issue. At least some of the potential risk factors for cysticercosis are present in the Hai DSS (pig-keeping, pork consumption, limited sanitation), although no significant associations with epilepsy were found. Possible factors contributing to the low prevalence of NCC (and possibly of epilepsy) may be the employment of zero-grazing animal husbandry techniques observed in the district, whereby animals are kept penned and fodder brought to them (Figure 2), the quality of meat inspection and food preparation locally, or the source of pork that is consumed within the district. Further investigation of such factors in this population are warranted, in order to understand the presence of the small number of cases of taeniasis and NCC identified in an environment where pig husbandry is potentially compatible with an absence of local transmission and to provide insights that may contribute to the prevention of NCC and, therefore, of epilepsy in areas of higher endemicity.

To diagnose NCC in PWE from the Hai DSS we combined clinical, serological and imaging findings according to diagnostic criteria that have previously been used in Africa [15, 18]. The prevalence of NCC on imaging in our cohort of PWE was 4.0%, and the WB serology used detected these cases with a sensitivity of only 33.3%, considerably lower than that seen with ELISA antibody serology in an endemic area of South Africa (54.5%), where the prevalence of NCC in PWE on CT imaging was 37% [34]. In the only other study from SSA outside of South Africa to correlate imaging and serology specifically to diagnose NCC in PWE, the sensitivity of serology for NCC on imaging varied between two different assays: 52.2% for EITB compared with 13.3% for WB [19]. The use of different assays makes the comparison of different studies difficult, with sensitivity varying widely according to assay and epidemiological context [10]. In addition, antigenic differences between different *T. solium* genotypes have been described [35], and these may influence both clinical presentation and diagnostic accuracy of serological tests [1, 16]. Based on our experience in Hai, we support the position that while serological screening has a value in defining the baseline prevalence of cysticercosis, it is not clinically useful in populations of low endemicity for *T. solium* or where neuroimaging is not available routinely [36].

There are some limitations to our study. While all socio-demographic data were collected from controls under supervision from the research doctor (EH), some these data were collected from PWE independently by field workers during the follow-up phase of the prevalence study, when patients were attending a local hospital for investigations. Non-attendance and other operational difficulties meant that these data were incomplete from nearly half of PWE overall (44.3%) and it is not clear what biases this may have introduced. A high refusal rate among potential controls meant that 1:1 and geographic matching were not achieved as intended. This may have led to an underestimation of the prevalence of seropositivity in the control group and thus an overestimation of the weak statistical association between seropositivity and epilepsy that was observed. For ethical and logistical reasons there was no control series of CT scans for comparison. Finally, the initial prevalence study only identified PWE with convulsive epilepsy, whether focal or generalised in onset. More subtle focal-onset seizures without secondary generalisation which were not detected by the study may also be due to acquired brain lesions such as NCC and so the true aetiological contribution of NCC to the burden of epilepsy in this population may be higher.

Summary and conclusions

Cysticercosis and NCC are present in the Hai DSS in northern Tanzania but at a low prevalence. Further study of the social and environmental factors that distinguish the Hai DSS from other areas of Tanzania and SSA where NCC is more highly endemic may help to target public health initiatives designed to reduce the burden of acquired epilepsy. Serological screening of PWE for cysticercal antibodies has a low sensitivity for identifying individuals with evidence of NCC on CT scanning in this population and therefore has limited utility in this setting beyond providing baseline estimates of exposure.

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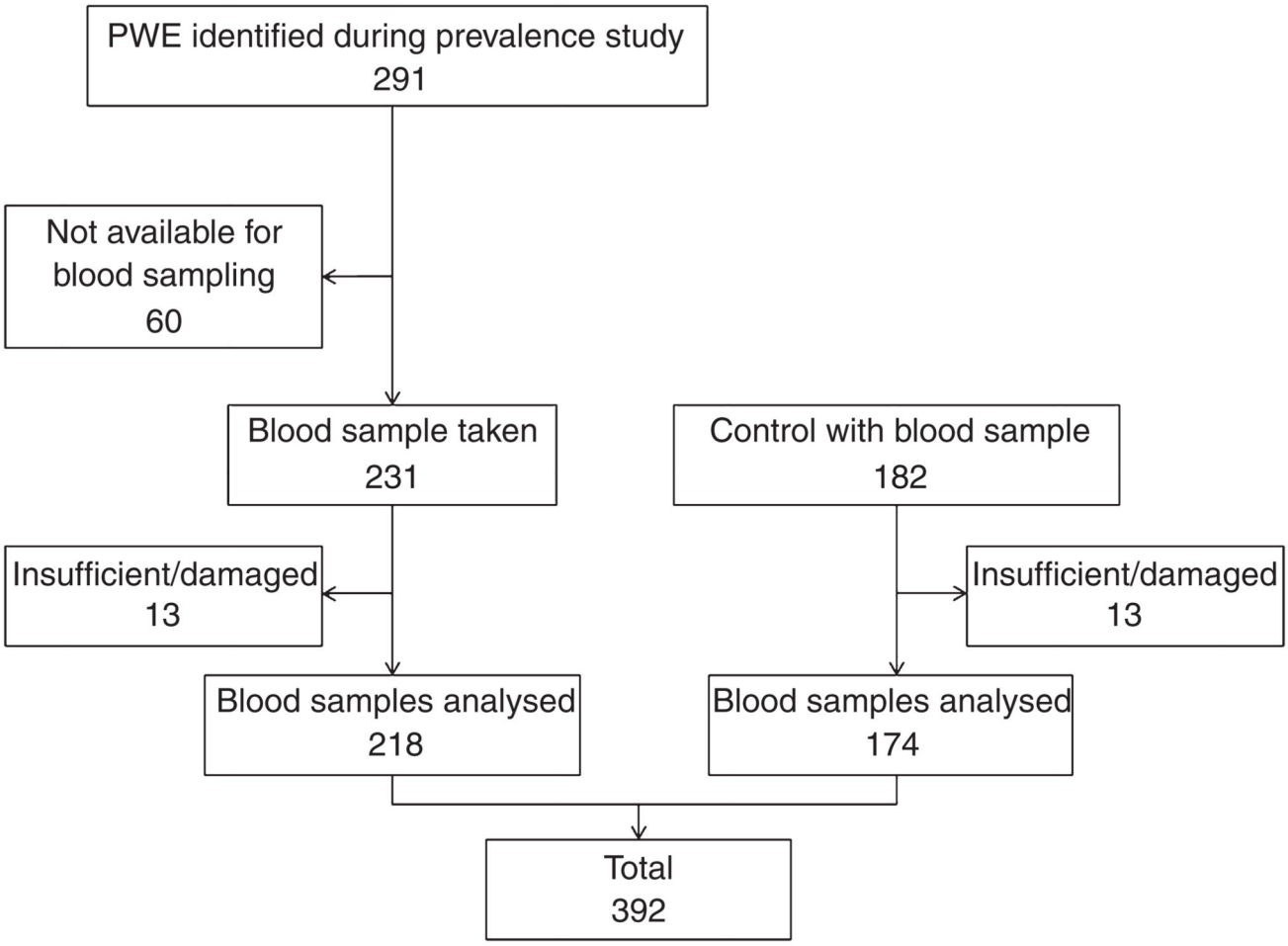

Figure 1.
Sources of blood samples analysed for *Taenia solium* antibodies.

Figure 2.
Zero-grazing pig husbandry in Hai.

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Table 1

Comparison of demographic features and risk factors for taeniasis/cysticercosis among people with epilepsy (PWE) and controls with available serology

		PWE (*N* = 218) *n* (%)*	Controls (*N* = 174) *n* (%)*	Statistical test
Age (years)	Median (IQR)	31.0 (23–45)	39.0 (25–50)	Mann–Whitney *U*-test = 15833.0
				$z = -2.812$
				$P = 0.005$
Sex	Males	117 (53.7)	79 (45.4)	$\chi^2(1) = 2.646$
	Females	101 (46.3)	95 (54.6)	$P = 0.104$
Tribe	Chagga	173 (80.8)	142 (83.0)	$\chi^2(1) = 0.309$
	Other	41 (19.2)	29 (17.0)	$P = 0.578$
Religion	Christian	175 (81.4)	143 (82.7)	$\chi^2(1) = 0.104$
	Muslim	40 (18.6)	30 (17.3)	$P = 0.748$
1° Education	Complete	109 (52.9)	134 (77.5)	$\chi^2(1) = 24.621$
	None/incomplete	97 (47.1)	39 (22.5)	$P < 0.001$
No. household occupants	Median (IQR)	5 (3–6)	5 (4–7)	$U = 13\,685.0$
				$z = 1.530$
				$P = 0.126$
Keeps pigs	Yes	17 (8.9)	11 (6.3)	$\chi^2(1) = 0.829$
	No	175 (91.1)	163 (93.7)	$P = 0.363$
Eats pork	Yes	72 (49.7)	85 (49.7)	$\chi^2(1) < 0.001$
	No	73 (50.3)	86 (50.3)	$P = 0.993$
Main water source	Piped/borehole	121 (82.9)	126 (75.0)	$\chi^2(1) = 2.887$
	River/open source	25 (17.1)	42 (25.0)	$P = 0.089$
Domestic sanitation	Indoor toilet	5 (3.4)	10 (5.8)	Likelihood ratio(2) = 1.043
	Pit latrine	138 (95.2)	159 (93.0)	$P = 0.594$
	No provision	2 (1.4)	2 (1.2)	

*Column totals within categories differ from *N* due to missing data.

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Table 2

Details of PWE in Hai with neurocysticercosis on CT and/or positive serology

										CT findings		Serology	
	Age	**Sex**	**Religion**	**Clinical seizure type**	**Pig***	**Pork†**	**Water‡**	**Toilet§**	**Persons/household¶**	**NCC lesions**	**Site(s)**	**r24**	**rES33**
1	17	M	Muslim	Focal	N/A	N/A	N/A	N/A	N/A	1	L frontal	No sample	
2	18	F	Christian	Focal	Y	Y	Piped	Pit latrine	4	2	Bilat. parietal	−	−
3	54	F	Christian	Focal	N	Y	Piped	Pit latrine	8	>5	Diffuse	+	+
4	46	F	Muslim	Focal	N	N/A	N/A	N/A	N/A	>5	Diffuse	−	−
5	31	F	Christian	Focal	N	N	Piped	Pit latrine	7	>5	Diffuse	+	−
6	23	F	Muslim	Focal	N	N	Piped	Pit latrine	3	1	L frontal	−	−
7	29	F	Muslim	Focal	N	N	Piped	Pit latrine	6	1	R temporal	−	−
8	17	F	Christian	Focal	N/A	N/A	N/A	N/A	N/A	1	R frontal	−	−
9	37	M	Christian	Undefined	N	N	Piped	Pit latrine	3	0	N/A	+	+
10	22	F	Christian	Focal	N/A	N	Piped	Pit latrine	7	0	N/A	−	+
11	74	M	Christian	Focal	N	N	Piped	Pit latrine	4	2	Bilat. frontal	+	−
12	45	M	Christian	Focal	Y	N/A	N/A	N/A	N/A	No scan		+	−

+: positive; −: negative; N/A: no data.

*Household that keeps pigs.

†Eats pork.

‡Main household water source.

§Household toilet facilities.

¶Number of persons in household.