

High frequency of *Taenia solium* antigen positivity in patients admitted for neurological disorders in the Rural Hospital of Mosango, Democratic Republic of Congo.

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Abstract

Background The epidemiology of human cysticercosis and neurocysticercosis, caused by the larval stage of the pork tapeworm *Taenia solium*, is not well known in the Democratic Republic of Congo (DRC). As part of an etiological study, we consecutively evaluated from 2012 to 2016 all patients older than 5 years admitted for neurological disorders (neurology cohort) at the rural hospital of Mosango, province of Kwilu, DRC. No neuroimaging was available. A similar study was conducted among patients presenting with persistent fever (> 7 days) during the same period in the same hospital. In both studies, etiological diagnosis relied on a systematic set of reference laboratory assays and on pre-established clinical case definitions. The aim of this post-hoc analysis was to determine the frequency of *T. solium* infection in these neurology and persistent fever cohorts and to explore its association with specific neurological presentations and final etiological diagnoses. **Methods** We conducted a descriptive and analytic study between the group of neurological syndrome patients and persistent fever based on the presence or not the cysticercosis IgG using the B158/B60 enzyme-linked immunosorbent assay and of the LDBIO Cysticercosis Western Blot IgG assay, respectively. **Results** For the neurology cohort, 340 samples (of 351 enrolled patients) were available for analysis (males: 46.8%; mean age: 38.9 years). *T. solium* antigen positivity was found in 43 participants (12.6%; 95% confidence interval [CI] 9.3-16.7%), including 9 of 60 (15%) patients with epilepsy. Of the 148 evaluated samples from the persistent fever cohort (males: 39.9%; mean age: 19.9 years), 7 had positive *T. solium* antigen (4.7%; 95% CI 1.9-9.5%; $P=0.009$ when compared to the neurology cohort). No significant association was found within the neurology cohort between positivity and clinical presentation or final diagnoses. Of note, the antibody-based assay was found positive in only four (1.3%) of the participants of the neurology cohort and in none of the persistent fever cohort. **Conclusions** *T. solium* antigen positivity was frequent in patients admitted with neurological disorders in the Kwilu province, DRC. Further neuroimaging studies should explore whether neurocysticercosis is prevalent in this region.

Introduction

Cysticercosis is an infection caused by the metacestode larval stage of the tapeworm *Taenia solium* that affects pigs and humans, in areas where sanitation and veterinary control are poor. Pigs act as intermediate hosts by ingesting *T. solium* eggs released in human feces. Humans are the only definitive host able to harbor adult tapeworms in the intestines, that may cause a rather mild illness called taeniasis. Humans, however, may also develop cysticercosis after ingestion of eggs, if the food/water or environment is contaminated with human fecal material, or by self-infection in case of adult worm carriage [1]. Larval cysts (also called cysticerci) may settle in different tissues (muscles, skin) but are preferentially localized in the central nervous system (brain and spinal cord), causing neurocysticercosis, a disease associated with major morbidity, poor quality of life and significant cost for the health-care system, particularly in low-resource settings [2,3]. Depending on the number, size, stage, and location of the cysticerci as well as the host's immune response, neurocysticercosis may cause a wide variety of neurological symptoms and signs, including seizures, headaches, focal deficits, psychiatric

manifestations and cognitive impairment [4–6]. On the other hand, some of the people carrying cysticerci in the central nervous system or in other locations may remain fully asymptomatic [2]. An accurate diagnosis of neurocysticercosis almost always requires a combination of epidemiological, clinical, imaging and serological information, as very few elements are fully diagnostic in isolation. Definitions of probable or definitive diagnosis of neurocysticercosis are based on a set of neuroimaging and clinical/exposure major and minor criteria, which have been recently revised by Del Brutto et al. [7]. Major neuroimaging criteria include cystic lesions, enhancing lesions, multilobulated cysts (all these lesions are usually referred to as active neurocysticercosis) and calcifications (referred to as inactive neurocysticercosis, in the absence of other active lesions). Well-standardized immunoassays are used as major “clinical/exposure criteria” and may detect either circulating *T. solium* antigens, reflecting the presence of living cysticerci in any tissue (current/active cysticercosis), or antibodies, which may be present in case of exposure and in current or past infection [8]. In low-resource settings, brain imaging and most immunoassays are usually not available or not affordable, making the definitive diagnosis of neurocysticercosis rarely possible [3,9].

Neurological disorders account for approximately 10% of all admissions in African rural hospitals [10–12]. However, the etiological spectrum has been hardly studied so far because of lack of diagnostic facilities [13]. To fill this knowledge gap, we investigated the infectious etiologies of neurological disorders in the rural hospital of Mosango, province of Kwilu, Democratic Republic of Congo (DRC) [14], as part of the NIDIAG project (“Neglected Infectious diseases DIAGnosis”, <https://nidiag.eu/>). In this setting where neuroimaging is not available, the contribution of neurocysticercosis in the neurological case load is unknown. *T. solium* is highly endemic in the Bas Congo province, west of the capital Kinshasa, and is suspected to be present in other parts of the country as well [15]. The aim of this study was to determine the frequency of positivity of antigen- and antibody-based *T. solium* immunoassays among the participants of the NIDIAG neurology study, as well as to explore the association with the clinical presentation and final diagnosis. A secondary objective was to determine the frequency of immunoassay positivity in another NIDIAG cohort of patients evaluated for persistent fever (> 7 days) in the same study hospital and during the same period.

Methods

Study participants and setting

We conducted a descriptive and analytic study between the group of neurological syndrome patients and persistent fever based on the presence or not the cysticercosis IgG using the western Blot test from LDBio. The rationale, objective, design, study population and setting of the NIDIAG neurology study have been described in detail previously (14). Briefly, all consecutive children older than five years and adults presenting with neurological disorders to the “Hôpital Général de Référence” (HGR) of Mosango, province of Kwilu were prospectively enrolled and evaluated. Entry criteria included any of the following: altered state of consciousness; change in sleep pattern; cognitive decline; changes in personality/behavior; recent (< 2 weeks) epileptic seizure; recent, severe and progressive headache; meningism; new onset

cranial nerve lesion; new onset sensory-motor focal deficit; and new onset gait/walking disorders. Participants underwent a systematic diagnostic workup including a microscopic examination of cerebrospinal fluid (CSF) unless this was contra-indicated. Neuro-imaging diagnostic methods were not available at the study site. A set of severe and treatable infections of the central nervous system (CNS) were considered as “priority infections” and were searched for systematically with pre-established reference methods (either on site, or in reference laboratories in Kinshasa, DRC or Antwerp, Belgium). Other diagnoses (of non-priority conditions) were made in 2016 by a panel of experts in neurology and infectious diseases, who reviewed the complete clinical case files and all laboratory results and followed pre-established case definitions [14]. Three hundred fifty-one patients were enrolled in the NIDIAG neurology study between 2012 and 2015.

In parallel, from 2013 to 2015, 300 children > 5 years and adults presenting to the same study hospital with persistent fever (defined as fever reported or documented for more than 7 days) were prospectively included in the NIDIAG persistent fever study. They also underwent a systematic diagnostic work-up to explore a pre-established set of priority severe and treatable etiologies.

Samples and laboratory procedures

All sera of the NIDIAG studies were shipped on dry ice to the Institute of Tropical Medicine, Antwerp and stored in the biobank at -80°C. For the present study, we selected all available serum samples from the entire NIDIAG neurology cohort and a subset of 150 samples from the NIDIAG persistent fever cohort (every other consecutive participant). In April 2018, these serum samples were processed for the detection of circulating cysticercal antigens and antibodies. The presence of circulating cysticercal antigen was measured in the serum using the in house B158/B60 enzyme-linked immunosorbent assay (Ag-ELISA). The optical density (OD) for each sample was divided by a cut-off OD value to obtain a ratio. The sample was considered positive for cysticercal antigens if the ratio was greater than 1.0 [16,17]. At this cut-off, the assay has a sensitivity of 90% to 100% to detect current cysticercosis and a specificity of 83% to 98% (9,18). To determine the presence of antibodies against *T. solium* infection, a commercial Western Blot assay using lentil-lectin purified glycoprotein antigens was used (Cysticercosis WB IgG, LDBIO Diagnostics, Lyon, France). This assay is considered to provide information on exposure to/current and past infection with *T. solium*, with a sensitivity of 98% and a specificity of 100% according to the manufacturer [19]. A result is considered positive if a minimum of two of the five bands react with the serum sample in the Western Blot. The laboratory technician who performed both *T. solium* assays was blinded to all clinical and diagnostic information. When the available serum volume was small, the antigen-detecting assay was prioritized.

Data analysis and reporting

Data were analyzed with SPSS software, version 25.0 (SPSS, Chicago, IL, USA). For both the NIDIAG neurology and persistent fever cohorts, the frequency of *T. solium* positivity was determined with a 95%

confidence interval (CI) and stratified by age group. Within the NIDIAG neurology cohort, the association of *T. solium* antigen positivity with clinical features and final diagnosis was also assessed. Baseline epidemiological characteristics and frequency data were compared between cohorts. Chi-square test or Fisher's exact test were used for categorical variables. Continuous variables were compared using parametric tests. All tests were two-sided and p values < 0.05 were considered statistically significant.

Ethical aspects

The study protocol was approved by the Institutional Review Board of the Institute of Tropical Medicine, Antwerp, Belgium and by the Ethics Committees of the University of Antwerp, Belgium (reference 11/50/400; 2012), and the Public Health School of Kinshasa, DRC (reference ESP/CE/016/2012). The study was registered at clinicaltrials.gov (identifier NCT01589289). Before enrolment, participants or their legal guardians gave written informed consent for study participation and for the future use of their stored clinical samples for further etiological or diagnostic research. For children between 12 and 18 years, in addition to the parental consent, informed assent was necessary for inclusion, in line with the DRC law.

Results

Serum samples were available for 340 out of the 351 participants (97%) of the NIDIAG neurology cohort. The mean age of this study population was 38.9 years [standard deviation: 17.7; range: 6-78]; and 159 out of 340 (46.8%) were male. Duration of neurological symptoms was more than two weeks in 190 (55.9%) of the evaluated patients and almost half had prior contact with a primary health care facility (Table 1). Severe headache was the most frequent complaint, followed by gait/walking disorders and seizure. Confirmed priority infections accounted for 84 (24.7%) of the final diagnoses while 156 (45.9%) cases were classified as non-communicable conditions, including mainly epilepsy and psychiatric disorders (Table 1). Death occurred in 26 patients (7.6%). The antigen-detecting assay was positive in 43/340 (12.6%; 95% CI 9.3-16.7%) participants of the NIDIAG neurology cohort. The antibody-detecting assay could be done in 314 samples, and was positive in four of them (1.3%; 95% CI 0.5-3.2%). All four cases were also *T. solium* antigen positive.

Within the neurology cohort, there were no differences regarding presenting features and final grouped or single diagnoses between *T. solium* antigen-positive and -negative participants (Table 1). There was only a trend for higher frequency of patients older than 20 years in the *T. solium* antigen-positive group ($P=0.05$).

In the neurology cohort, the frequency of *T. solium* antigen positivity was 12.6% in patients with reported/documented fever and 13.7% in patients without fever ($P=0.2$). Slight non-significant variations in frequency were observed between the presenting neurological symptoms in the whole cohort or when restricted to non-febrile patients. *T. solium* antigen was positive in 8/84 (9.5%) of patients with confirmed priority infection and in 22/156 (14%) of those finally diagnosed with non-communicable conditions, but

this difference was not statistically significant ($P=0.3$). Antigen positivity was observed in 9 of 60 (15%) patients diagnosed with epilepsy.

Of the 150 samples obtained from the patients with persistent fever, 148 could be analyzed with both antigen- and antibody-based tests. Of them, 59 (39.9%) were male (Table 2). Mean age was 19.9 years (standard deviation: 16.2; range: 6-72) in this cohort, and was significantly lower than that of the neurology cohort ($p < 0.001$). *T. solium* antigen was positive in 7/148 (4.7%; 95% CI 1.9-9.5%). No single case of positive *T. solium* antibody assay was found. As shown in Table 2, the frequency of *T. solium* antigen positivity was significantly higher in the neurology compared to the persistent fever cohort ($P=0.009$; odds ratio 2.9; 95% confidence interval 1.3-6.6). When we stratified by age, the frequency of positivity remained higher in the neurology cohort, but this was not statistically significant anymore.

Discussion

In this post-hoc analysis of a prospective cohort of patients presenting with neurological disorders in a rural hospital of Central Africa, we found that about 13% had evidence of circulating *T. solium* antigen in serum. There were no clear associations between presenting symptoms or final diagnoses and seropositivity for *T. solium* antigen. The frequency was significantly higher than that found in another study that ran in parallel and evaluated patients with persistent fever (approximately 5%), but the statistical significance was not retained when comparisons between cohorts were stratified by age groups (with smaller sample size). Surprisingly, the antibody-based immunoassay was positive in only 1.3% of the neurological patients and in none of the persistent fever cohort.

This exploratory study has many limitations, most of which were largely acknowledged in previous publications [14,20,21]. The use of patients rather than a sample of the general population is one of the limitations of the study as it does not enable the magnitude of the underlying problem to be estimated. A complete diagnostic workup was restricted to a set of priority infections for both the neurology and the persistent fever studies. In particular for the neurology study, the etiological workup was limited by the absence of advanced neurological investigations in this low-resource hospital. Consequently, no causative link can be formally established between the serological markers of *T. solium* infection and the neurological presentation in the absence of brain/spinal imaging. Also, the persistent fever cohort was opportunistically used for comparison, but cannot be considered as a “control” group as such since the distribution of age groups was different. Finally, another important limitation is the surprisingly low prevalence of *T. solium* antibodies in the neurology cohort, while one would have expected a proportion of antibody-positive participants, indicating exposure to *T. solium* eggs, larger than that of antigen positivity. A possible explanation is that some degradation of the *T. solium* immunoglobulins has inflated the false negative rate when the antibody assay was performed in 2018, while blood sampling took place between 2012 and 2015. However, transport and storage were rigorously monitored during the study and other serological investigations on the same stored samples did provide plausible results [22]. Alternatively, this may have been related to differences in the circulating strains of *T. solium*, parasitic load or host characteristics compared to settings where the antibody-detection assay was validated [23]. A failure of

the LDBIO assay itself is unlikely since it performed well with positive and negative controls. However, sensitivity of this commercial assay has been reported in one study as substantially inferior to that of the reference Centers of Disease Control-developed enzyme-linked electroimmunotransfer blot (CDC-EITB), i.e. 13.3% versus 52.2% among 23 CT-confirmed neurocysticercosis cases tested [24]. On the other hand, in a recent Mexican study on 58 NCC patients, the sensitivity of the LDBIO EITB was slightly higher (71.4%) than that of the CDC-EITB (66.1%) (25). These discrepancies between EITB test sensitivities need further investigation on a larger number of samples.

The African continent reports the highest burden of human cysticercosis in the world, with pooled prevalence of circulating *T. solium* antigens estimated at 7.30% (95% CI 4.23-12.31) and of antibodies at 17.37% (95%CI 3.33-56.20) in community-based epidemiological surveys [25]. In DRC, the epidemiology of human and porcine cysticercosis is poorly understood. Some surveys in the animal markets of Kinshasa have revealed active cysticercosis in pigs originating from different DRC provinces [18], including in more than 30% of those coming from Bandundu (the former name of the Kwilu province). Very high prevalence of human cysticercosis (proportion of *T. solium* antigen positivity up to 21%) has been reported in the only community-based survey performed so far, in the province of Bas Congo [15].

The prevalence of neurocysticercosis remains unknown in most low-resource settings, since neuroimaging is required to establish the diagnosis [26]. The frequency of probable and definitive neurocysticercosis has been mainly investigated in patients with epilepsy, in whom the pooled estimate obtained from brain CT Scan-based studies was 30%, globally [26] and in Latin America [27]. Additional studies performed later on in Africa revealed that the proportion of neurocysticercosis in patients with epilepsy varied a lot according to the setting and could range from 15% to 50% [24,28–30].

Diagnostic accuracy studies of antigen- and antibody-based assays for the specific diagnosis of neurocysticercosis (based on CT findings) in Africa have been limited to small case series. Using Del Brutto's definition of probable or definitive neurocysticercosis in patients evaluated for epilepsy in Zambia, Gabriël et al. found a sensitivity of 44% (15 positive results/34 cases) for *T. solium* antigen, when using a cutoff of 1.0, and a specificity of 90% (9). When restricting the analysis to patients with active neurocysticercosis (i.e. presence of cystic lesions, n=6), sensitivity was 100% and specificity 84%. Antibody-based assays are usually reported as highly sensitive for neurocysticercosis in patients with more than one viable cystic lesion, but performance is much lower in cases of single lesions or of calcifications only. The specificity of antibody-based tests for neurocysticercosis is variable since distinction with previous exposure or cured infection cannot be made [(23)]. Based on all these considerations, the sizeable proportion of participants with positive *T. solium* antigen in both cohorts demonstrates that active cysticercosis and neurocysticercosis are endemic in the study area, since false-positive results are infrequent for both conditions. Also, the high frequency of antigen positivity in patients with neurological disorders is compatible with the hypothesis that this infection plays some causal role [4,31]. It is worth reminding in addition that neurocysticercosis tends to become clinically apparent when the cystic lesions degenerate, through local inflammatory reactions, while active cysts alone usually cause little neurological symptoms [32].

Neuroimaging is absolutely necessary not only to accurately diagnose neurocysticercosis, but also to safely manage the potential risk of clinical deterioration due to anti-helminthic treatment (albendazole and/or praziquantel). While proven useful for epidemiological surveys and under study for public health interventions (such as mass drug administration with anti-helminthic drugs in endemic regions), the utility of immunoassays is more questionable for clinical care, since no therapeutic decision can exclusively rely on their results [23,33]. Antigen- or antibody-based assays, whenever available at the point-of-care [34,35], could however be explored as an operational screening tool to select the subset of neurological patients who might benefit most from neuroimaging(37). Since such investigations would be difficult to obtain and expensive in rural Congo, choosing assays or cutoffs with high specificity to diagnose active neurocysticercosis (the main form responsive to anti-helminthic treatment) needs to be prioritized, in order to minimize the number of unnecessary referrals. Prior to such a study however, adequate treatment of neurocysticercosis has to be made available in African low-resource hospitals [3].

Conclusion

In this retrospective analysis of hospital-based neurology and persistent fever cohorts in the Kwilu province of DRC, *T. solium* antigen positivity was frequent (about 13% and 5%, respectively), confirming that this infection is prevalent in the region. Although the causal link with neurocysticercosis could not be formally established, our findings suggest that *T. solium* infection may contribute to the neurological case load in Central African areas. Further research should aim at performing brain imaging in neurological patients found with circulating antigens to fully characterize the spectrum of *T. solium*-associated morbidity in rural DRC.

Declarations

- Ethics approval and consent to participate

As mentioned under materials and Methods, ethics approvals were obtained from the Institutional Review Board of the Institute of Tropical medicine and the Ethical Committee of the University Hospital, Antwerp, Belgium as well as the School of Public Health of the University of Kinshasa, DR Congo. All study participants signed an informed consent before inclusion in this studies and accepted that additional investigations could be performed later on retrospectively on their samples for etiological purposes.

- Consent for publication

All participants consented for publication of the study data.

- Availability of data and material

The Institute of Tropical Medicine of Antwerp, Belgium (sponsor of this study) is exploring the public repositories that allow making all material and data available with sufficient security. Meanwhile, the dataset is available on request.

- Competing interests

The authors report no conflict of interest

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- Authors' contributions

Designed research: EB, MB, FC, JJ, PL, CY, ASW

Enrolled patients, performed and registered clinical diagnosis: DM, EB, CY, ASW

Performed laboratory experiments: JRLK, BB, PD, SG

Analyzed the data: EB, KV, PD, SG

Wrote the paper: EB, DM, MB, JJ, PD, SG, FC, CY, ASW, KV

Agree with manuscript results and conclusions: all authors

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Abbreviations

CNS : Central Nervous System

CSF : Cerebrospinal fluid

DRC : Democratic republic of Congo, The

ELISA : Enzyme-Linked Immunosorbent assay

HGR : Hôpital Général de Référence

NIDIAG : Neglected Infectious diseases DIAGnosis

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Tables

Table 1: Baseline features, final diagnoses and outcome of 340 patients of the NIDIAG neurology cohort with available *T. solium* antigen results

| | Total participants evaluated (n=340) n (%) | TS antigen negative participants (n=297) n (%) | TS antigen positive participants (n=43) n (%) | P |
|---|--|--|---|----------|
| <u>Features at presentation</u> | | | | |
| Male gender | 159 (46.8) | 137 (46.1) | 22 (51.2) | 0.5 |
| Age > 20 years | 270 (79.4) | 231 (77.8) | 39 (90.7) | 0.05 |
| Prior contact with primary care facility | 159 (46.8) | 141 (47.5) | 18 (41.9) | 0.4 |
| Neurological symptoms > two weeks | 190 (55.9) | 168 (56.6) | 22 (51.2) | 0.5 |
| Fever reported/documentated | 99 (29.1) | 89 (30.0) | 10 (23.3) | 0.3 |
| Severe headache | 156 (45.9) | 136 (45.8) | 20 (46.5) | 0.9 |
| Severe headache without fever | 101 (29.7) | 86 (29.0) | 15 (34.9) | 0.4 |
| Gait/walking disorders | 97 (28.5) | 86 (29.0) | 11 (25.6) | 0.6 |
| Seizure | 84 (24.7) | 73 (24.6) | 11 (25.6) | 0.8 |
| Focal sensory-motor deficit | 77 (22.6) | 67 (22.6) | 10 (23.3) | 0.9 |
| Cognitive and/or behavior disturbance | 72 (21.2) | 60 (20.2) | 12 (27.9) | 0.2 |
| Altered state of consciousness | 69 (20.3) | 61 (20.5) | 8 (18.6) | 0.7 |
| <u>Final diagnoses</u> | | | | |
| Confirmed priority infections | n (%) 84 (24.7) | n (%) 76 (25.6) | n (%) 8 (18.6) | - 0.3 |
| Confirmed and suspected infections | 119 (35.0) | 107 (36.0) | 12 (27.9) | 0.2 |
| Non-communicable conditions | 156 (45.9) | 134 (45.1) | 22 (51.2) | 0.4 |
| Epilepsy | 60 (17.6) | 51 (17.2) | 9 (20.9) | 0.5 |
| Psychiatric disorders | 53 (15.6) | 47 (15.8) | 6 (14.0) | 0.7 |
| Myelo-radiculo- neuropathic syndromes | 37 (10.9) | 30 (10.1) | 7 (16.3) | 0.2 |
| Cerebrovascular accident | 23 (6.8) | 20 (6.7) | 3 (7.0) | 0.9 |
| <u>Outcome</u> | | | | |
| Death | n (%) 26 (7.6) | n (%) 23 (7.7) | n (%) 3 (7.0) | 0.8 |

TS denotes *Taenia solium*

Table 2: Epidemiological features and frequency of *T. solium* antigen and antibody positivity in the neurology and persistent fever cohorts evaluated at the rural hospital of Mosango, Democratic Republic of Congo

| | Neurological cohort (n=340) | Persistent fever cohort (n=148) | <i>P</i> |
|--|--------------------------------|------------------------------------|----------|
| Epidemiological data | | | |
| Male gender, n (%) | 159 (47) | 59 (40) | 0.1 |
| Mean age (SD), years | 39.9 (17.7) | 19.9 (16.2) | < 0.001 |
| Positive <i>T. solium</i> antigen assay | | | |
| Total group, n (%) | 43 (12.6) | 7 (4.7) | 0.009 |
| Age group ≤ 20 years, n/n (%) | 4/70 (5.7) | 3/92 (3.3) | 0.4 |
| Age group 21-40 years, n/n (%) | 17/104 (16.7) | 3/35 (8.6) | 0.4 |
| Age group > 40 years, n/n (%) | 22/166 (13.3) | 1/21 (4.8) | 0.4 |
| Positive <i>T. solium</i> antibody assay | | | |
| Total group n/n (%) | 4/314 (1.3) | 0/148 (0) | 0.3 |

Note: SD denotes standard deviation