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Taenia solium Neuro/-zystizerkose und Täniose in Tansania

- Klinisch-epidemiologische Untersuchungen in speziellen Kohorten -

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Ich, Veronika Schmidt, erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema „*Taenia solium* Neuro/-zystizerkose und Täniose in Tansania: Klinisch-epidemiologische Untersuchungen in speziellen Kohorten“ selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

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Vomp, den 08.07.2021

Mag. Veronika Schmidt

Inhaltsverzeichnis

Abkürzungsverzeichnis

Ag	Antigen
Ak	Antikörper
AIDS	Erworbenes Immunschwächesyndrom („Acquired Immune Deficiency Syndrome“)
ASTMH	American Society of Tropical Medicine and Hygiene
CD4+	CD4+-Rezeptor („Cluster of Differentiation 4+“)
CT	Computertomografie
DALYs	Disability Adjusted Life Years
EITB	Enzyme-linked Immunoelectrotransfer Blot
ELISA	Enzyme-linked Immunosorbent Assay
FAO	Ernährungs- und Landwirtschaftsorganisation der Vereinten Nationen
FERG	Foodborne Diseases Burden Epidemiology Reference Group der WHO
HAART	Antiretrovirale Therapie („Highly Active Antiretroviral Therapy“)
HIV	Humanes Immundefizienz-Virus
IDSA	Infectious Diseases Society of America
LLGP-EITB	Lentil-Lectin aufgereinigter Glykoprotein-EITB
MDA	Massenchemotherapie („Mass Drug Administration“)
MRT	Magnetresonanztomografie
NCC	Neurozystizerkose
NTD	Vernachlässigte Tropenerkrankung („Neglected Tropical Disease“)
NZD	Vernachlässigte Tropenzoonose („Neglected Zoonotic Disease“)
TSCT	*T. solium* Neuro-/zystizerkose und Täniose
WHO	Weltgesundheitsorganisation

1 Einleitung

Die *T. solium* Neuro-/zystizerkose und Täniose (TSCT) ist ein parasitärer Erkrankungskomplex mit einem Verbreitungsschwerpunkt in den Endemieländern auf der südlichen Hemisphäre. Durch den zunehmenden internationalen Reiseverkehr, Migration und vereinzelt persistierende endemische Gebiete auf der nördlichen Hemisphäre besitzt sie jedoch globale Bedeutung [1, 2]. Die TSCT zählt zu den im Jahr 2017 von der Weltgesundheitsorganisation (WHO) ergänzten 21 vernachlässigten Tropenerkrankungen („neglected tropical diseases“, NTDs) [3]. Zusammen mit Echinokokkose, Tollwut und durch Nahrungsmittel übertragenen Infektionen mit Saugwürmern (Trematoden) zählt sie darüber hinaus zu den vernachlässigten zoonotischen Erkrankungen („neglected zoonotic diseases“, NZDs) [4].

Ein im Jahr 2015 von der WHO Foodborne Diseases Burden Epidemiology Reference Group (FERG) erstellter Report führt *T. solium* in einer Gruppe von 31 Bakterien, Viren, Parasiten, Toxinen und Chemikalien, welche für lebensmittelbedingte Todesfälle ursächlich sind, an. Die TSCT wurde darin mit einem Median von 370.710 globalen Erkrankungsfällen, 28.114 Todesfällen und 2.788.426 DALYs („Disability Adjusted Life Years“) angegeben. Die relative Beteiligung an der Anzahl der DALYs war vor allem für viele afrikanische, südamerikanische und südostasiatische Regionen beträchtlich [5]. Diese Daten unterstreichen das Nord-Süd-Gefälle dieser parasitären Erkrankung, aber auch die enge Assoziation mit Ressourcen- und Strukturmangel sowie unzureichenden Hygiene- und Lebensbedingungen in den am meisten betroffenen Regionen.

Im Folgenden wird ein Überblick über die Bedeutung des Schweinefinnenbandwurms, *T. solium*, die durch diesen hervorgerufenen Erkrankungsformen sowie deren Bedeutung, Verbreitung, Diagnostik und Therapie gegeben.

1.1 *Taenia solium* – der Schweinefinnenbandwurm

Der Schweinefinnenbandwurm, *T. solium*, ist ein Endoparasit, dessen Lebenszyklus den Hauptwirt Mensch und den Zwischenwirt Schwein umfasst (Abbildung 1).

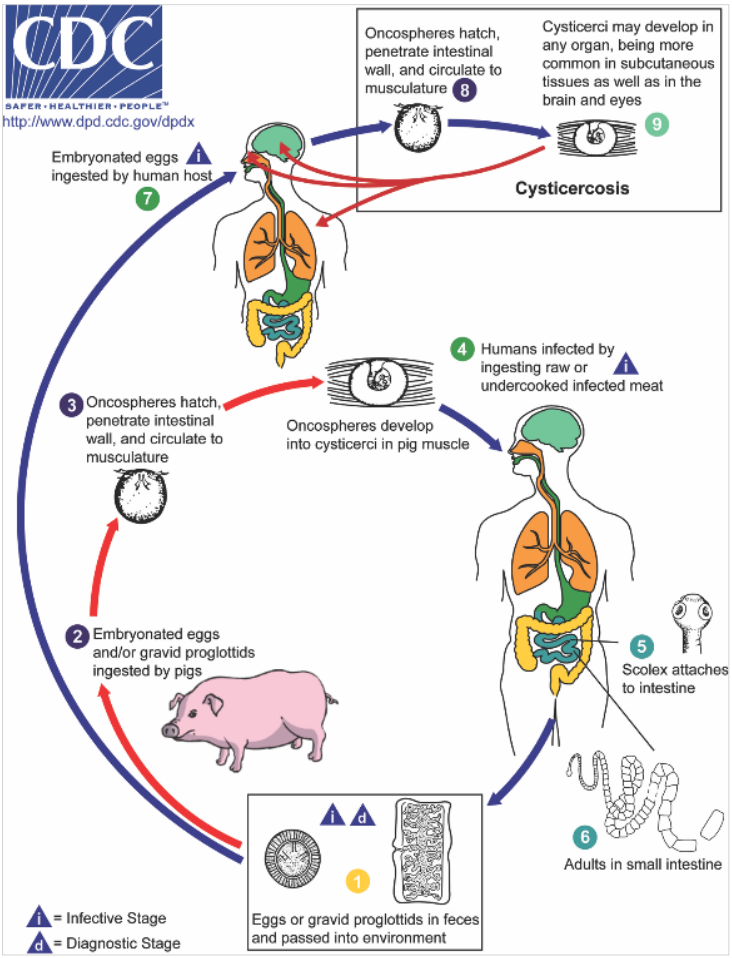

Abbildung 1. Lebenszyklus von *T. solium* mit seinem Hauptwirt Mensch und Zwischenwirt Schwein; der Mensch kann für diesen Parasiten zusätzlich auch als Fehlwirt fungieren [6]

Der adulte Wurm ist von weißlicher bis gelblicher Farbe und erreicht eine Länge von 2 bis 4 m. Charakteristisch ist sein Kopf (Skolex) mit vier Saugnäpfen und einem Hakenkranz (Rostellum), welcher aus kleinen und größeren Häkchen besteht (Abbildung 2). Es folgen der Halsteil (Strobila) und bis zu 1.000 Proglottiden, die jeweils einen tubulären Uterus mit sieben bis zwölf pathognomischen Seitenästen sowie über 50.000 Eiern beinhalten. Meist ist nur ein einzelner adulter Wurm im Darm zu finden.

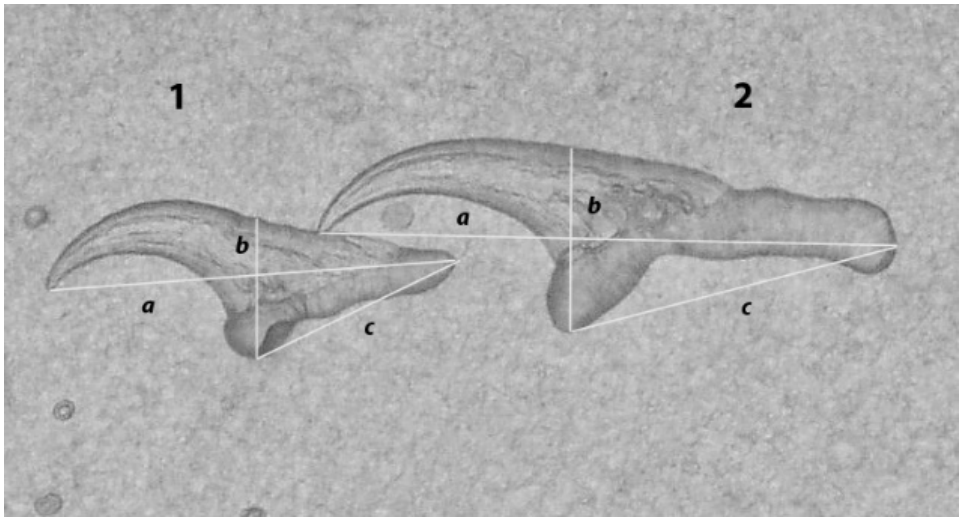

Abbildung 2. Natives Mikroskopiebild der Haken des inneren (1) und äußeren (2) Hakenkranzes (Rostellum) von *T. solium* (Präparation und Bild: Veronika Schmidt)

Der adulte Wurm parasitiert im Dünndarm des Menschen, welcher pro Tag zwischen sechs bis neun nicht bewegliche Proglottiden zusammen mit dem Stuhl in die Umwelt ausscheidet. Diese Proglottiden und Eier werden von Schweinen – als natürliche Koprophagen – aufgenommen. Im Schweinemagen schlüpfen die Larven (Onkosphären) und durchdringen die Magen- und obere Dünndarmmukosa. Über die Blutbahn gelangen diese dann in die Skelett-, aber auch glatte Muskulatur und es bildet sich das charakteristische zystische Finnenstadium (*Cysticercus cellulosa*) aus (porzine Zystizerkose) (Abbildung 3 und Abbildung 4) [7, 8].

Abbildung 3. Mit *T. solium* Zystizerken infestierter Skelettmuskel eines Hausschweins (*Sus scrofa scrofa*) (Präparation und Bild: Veronika Schmidt)

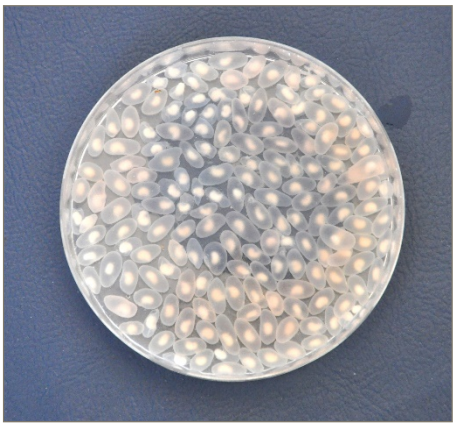

Abbildung 4. *T. solium* Zystizerken mit Skolexanlage in Phosphatpuffersaline [9]

Auch beim Schwein kann die Blut-Hirn-Schranke durch die Larven überwunden werden und es können sich Zystizerken im Gehirn ausbilden (Neurozystizerkose [NCC]) (Abbildung 5 und Abbildung 6).

Abbildung 5. Querschnitt eines in Formalin konservierten Gehirns eines Hausschweins mit intraparenchymatösen *T. solium*-Zystizerken (Präparation und Bild: Veronika Schmidt)

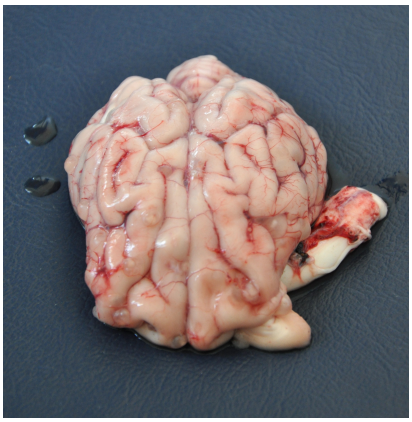

Abbildung 6. Präpariertes Gehirn eines Hausschweins mit subparenchymatösen *T. solium*-Zystizerken (Präparation und Bild: Veronika Schmidt)

Bei Aufnahme von rohem oder halbrohem Schweinefleisch gelangen die Zystizerken in den menschlichen Magen und Dünndarm. Die darin enthaltene Skolexanlage evaginiert aus der Zyste und es beginnt wiederum das Wachstum eines adulten Bandwurms (Täniose). Durch mangelnde Körperhygiene, kontaminiertes Wasser oder Lebensmittel können *T. solium* Eier jedoch fäkal-oral auch direkt von Mensch zu Mensch übertragen und entweder selbst oder von anderen wieder-/aufgenommen werden. In diesem Fall fungiert der Mensch für den Parasiten als Fehlwirt. Wie beim Zwischenwirt Schwein dringen nun die Onkosphären durch die Magen- und Dünndarmmukosa und wandern über die Lymph- und Blutbahn durch den Körper. Dort setzen sie sich schließlich als Zystizerken vor allem im Gehirn, aber auch in Rückenmark, Auge, Herz, Skelettmuskulatur oder im subkutanen Bindegewebe (Neuro-/zystizerkose) ab [10]. Andere Manifestationsorte wie z. B. in der Zunge oder den Tränendrüsen sind möglich, aber vergleichsweise selten [11, 12].

1.2 Globale Verbreitung und Risikofaktoren der *T. solium* Neuro-/zystizerkose und Täniose

Die TSCT ist als Erkrankungskomplex weltweit verbreitet. Denn auch in nicht endemischen Gebieten hat die Infektion mit *T. solium* als Reiseerkrankung und im Kontext von Migrationsbewegungen Bedeutung [13–16]. Im Jahr 2016 veröffentlichte die WHO eine Karte der Länder, die bisher als endemisch gelten (Abbildung 7) [17, 18]. Hier zeigt sich, dass die Hochendemieländer vor allem in Zentral- und Lateinamerika, Subsahara-Afrika sowie in Südostasien zu finden sind. Vereinzelt gibt es auch endemische Gebiete in Osteuropa (z. B. Rumänien, Slowakei und Kroatien), im nördlichen Indien und in China. Zahlreiche Länder wurden darüber hinaus als potenziell gefährdet eingestuft, da hier autochthone Fälle gemeldet wurden und/oder alle Voraussetzungen für einen vollständigen Lebenszyklus von *T. solium* vorhanden sind. Darunter finden sich auch europäische Länder wie Spanien, Österreich, Polen und Ungarn [17, 18]. Die Datenlage in den meisten Ländern ist jedoch nicht ausreichend, um daraus genaue flächendeckende Schlüsse ziehen zu können. Dieser Missstand wird auch dadurch begünstigt, dass bisher für die TSCT in kaum einem Land eine Meldepflicht besteht [15, 16].

In den Endemieländern der südlichen Hemisphäre sind vor allem Seroprävalenzdaten zur Zystizerkose vorhanden, jedoch kaum Daten zur Neurozystizerkose, da erforderliche Computertomografen (CT) für diese Diagnosestellung meist nicht vorhanden sind [1, 19]. Auch genaue Daten zur *T. solium* Täniose sind aufgrund fehlender speziesspezifischer Labordiagnostik selten verfügbar. Hier kommt es häufig zu einer Aggregation mit Fällen von *T. solium, T. saginata* und *T. asiatica* in der Literatur unter dem Sammelbegriff „Täniose“, welcher keine Rückschlüsse auf die Prävalenz der einzelnen Spezies zulassen.

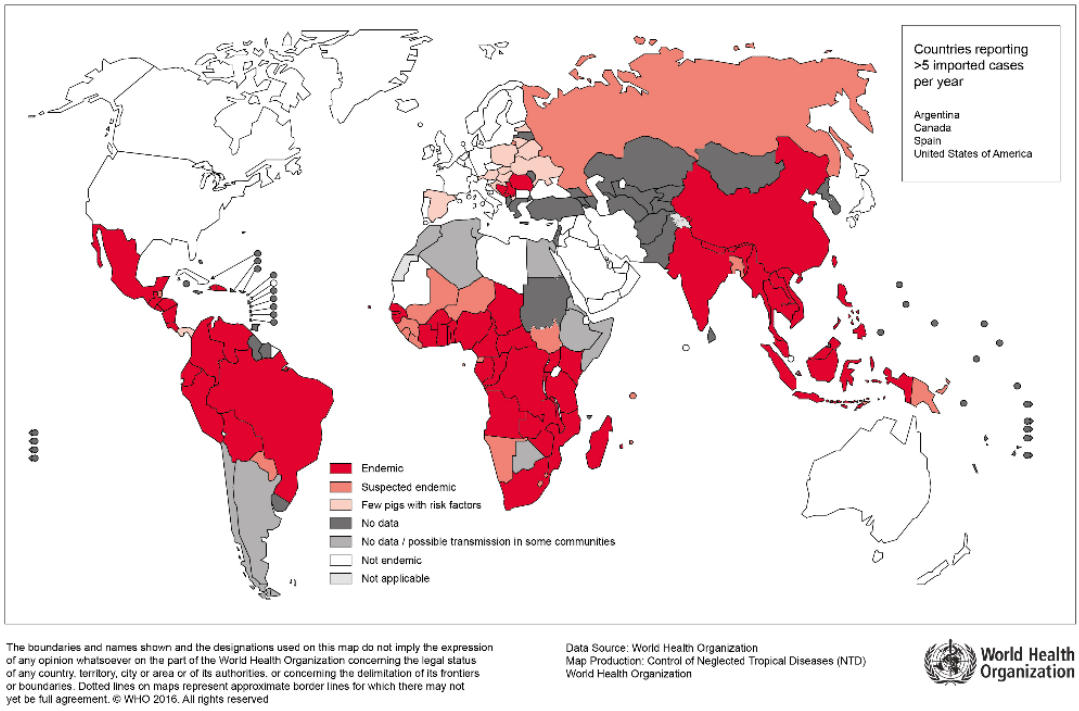

Abbildung 7. Verbreitungsgebiete von *T. solium* (World Health Organization, 2015) [17, 18]

Für die endemischen Gebiete Lateinamerikas berechneten Coral-Almeida und Kollegen (2015) eine mittlere Seroprävalenz von zirkulierendem *T. solium* Zystizerkose-Antigen (Ag) (basierend auf Ag-Enzyme-linked Immunosorbent Assay [ELISA])-Resultaten) von 4,08 % (95 % CI [2,77–5,95 %]) und von zirkulierenden Antikörpern (Ak) (basierend auf Enzyme-linked Immunoelectrotransfer Blot [EITB]-Resultaten) von 13,03 % (95 % CI [9,95–16,88 %]). Für Asien – mit einer deutlich schlechteren Datenlage – wurde eine Prävalenz von 3,98 % (0,95 % CI [2,81–5,61 %]) für Zystizerkose-Ag und von 15,68 % (0,95 % CI [10,25–23,24 %]) für Zystizerkose-Ak berechnet [20]. Alleine für China wird geschätzt, dass derzeit drei Millionen Patienten mit Zystizerkose infiziert sind [1, 21, 22].

In Afrika sind die Endemiegebiete vor allem südlich der Sahara zu finden. Die meisten Daten liegen hier für Sambia, die Demokratische Republik Kongo, Kamerun, Burkina Faso, Südafrika, Tansania und Kenia vor [1]. Hier wurde eine durchschnittliche Prävalenz für zirkulierende Zystizerkose-Ag von 7,30 % (95 % CI [4,23–12,31 %]) und für Zystizerkose-Ak von 17.37 % (95 % CI [3,33–56,20 %]) aufgezeigt [1, 20]. Auffallend in diesem Zusammenhang ist, dass die hier zugrundeliegenden Querschnittsstudien ausschließlich im ländlichen Raum durchgeführt wurden und spezielle Kohorten (wie urbane Populationen, mit HIV co-infizierte Patienten, Kinder und Jugendliche etc.) bislang kaum untersucht wurden.

Die Anzahl von NCC-bedingten Epilepsie-Fällen in Subsahara-Afrika wurde von Winkler et al. (2013) auf 0,76 bis 2,46 Millionen geschätzt und die der symptomatischen (dies inkludiert die Hauptsymptome epileptische Anfälle und Kopfschmerzen) NCC-Fälle gesamt immerhin auf 0,95 bis 3,08 Millionen [23]. Für Tansania sind einige wenige Daten für NCC aus vorangegangenen Studien bekannt. Auf diese wird genauer in den beiden Veröffentlichungen, die dieser Dissertation zugrunde liegen, eingegangen (Anhang 1 und 2).

Prävalenzdaten zur *T. solium* Täniose (Ak und Kopro-Ag) variieren in endemischen Gebieten stark, da es hier typischerweise zu einer Herdbildung („cluster“) kommt [24, 25]. In einer Metaanalyse wurde für Asien eine Prävalenzspanne von 0 % (95 % CI [0–1,74 %]) bis 3.02 % (95 % CI [1,90–4,53 %]), für Lateinamerika von 0.24 % (95 % CI [0,03–0,87 %]) bis 17.25 % (95 % CI [14,55–20,23 %]) und für Afrika von 0 % (95 % CI [0–1,62 %]) bis 13.9 % (95 % CI [12,39–15,47 %]) dargelegt [20].

In Bezug auf die Verbreitung der TSCT geht von Bandwurmträgern und von infizierten Schweinen das größte Risiko aus; NCC-Patienten tragen nicht zur Verbreitung bei, sofern sie nicht zusätzlich Träger eines adulten Wurms sind [26]. Zusätzliche Risikofaktoren, die für die Übertragung und Verbreitung von *T. solium* bedeutsam sind, sind ein geringer Standard an Körper- und Lebensmittelhygiene, fehlende oder mangelhaft konstruierte Latrinen und Abwassersysteme, Schweinehaltungssysteme mit teilweiser oder gänzlicher Freilandhaltung, das Fehlen einer Fleischbeschau und Qualitätskontrolle von Schweinefleischprodukten sowie generell die fehlende Kenntnis über diese parasitäre Erkrankung [27–30].

1.3 Pathogenese und Krankheitsbild der *T. solium* Neuro-/ zystizerkose und Täniose

Eine NCC ist durch das Einwandern von *T. solium* Larven in das Gehirn (*kraniale NCC*) und/oder das/den Rückenmark/-kanal (*spinale NCC*) sowie die dortige Ausbildung des Zystenstadiums gekennzeichnet. Beide Ausprägungsformen der NCC können symptomfrei verlaufen, aber auch mit einer milden bis schweren Symptomatik einhergehen [31].

Das klinische Erscheinungsbild der *kranialen NCC* variiert entsprechend der betroffenen Hirnareale, der Größe und Anzahl der Zystizerken sowie dem Vorhandensein und Ausmaß einer umgebenden Entzündungsreaktion (= Ödem). Das Vorhandensein und die Ausprägung einer solchen Reaktion hängen wiederum maßgeblich von dem Entwicklungsstadium der Zystizerken (aktiv, degenerierend oder kalzifiziert) sowie deren intra- und/oder extraparenchymatöse Lokalisation ab. Klinische Symptome treten häufig erst Jahre nach der Infektion auf (meist nach drei bis fünf Jahren) [31, 32]. Vor allem die intraparenchymatöse NCC äußert sich häufig mit epileptischen Anfällen (80 % der symptomatischen Fälle) [33]. Einem Bericht aus Mexiko zufolge liegt in endemischen Regionen in bis zu 40 % der Epilepsiefälle, die sich in medizinischer Behandlung befinden, eine NCC zugrunde [34]. Bei der kranialen Form können häufig progressive chronische Kopfschmerzen, aber auch fokale neurologische Defizite, vaskuläre Schäden, Schlaganfälle sowie kognitive Defizite und Depression auftreten [31–33]. Multiple Läsionen finden sich vor allem bei der intraparenchymatösen NCC (Abbildung 8). Bei Patienten unter 30 Jahren, Patienten aus Indien sowie Reisenden aus nicht endemischen Ländern finden sich häufig nur vereinzelte Läsionen im Gehirn [36, 37] (Abbildung 9). Die extraparenchymatöse NCC (subarachnoidal oder intraventrikulär) kann zu einem potenziell lebensbedrohenden Anstieg des Hirndrucks durch eine

partielle oder totale Blockade des Flusses des *Liquor cerbrospinalis* sowie zur Ausbildung eines Hydrozephalus führen [1, 36].

Abbildung 8. CT-Bild eines symptomatischen NCC-Patienten mit multiplen intraparenchymatösen kalzifizierten Läsionen [35]

Abbildung 9. CT-Bild eines symptomatischen NCC-Patienten mit einem fokalen Ödem und einer isodensen Läsion in der weißen Substanz des linken Frontallappens [35]

Bei ca. 1 bis 5 % der NCC-Fälle liegt die Lokalisation der Zystizerken im Rückenmarksbereich [1]. Die *spinale NCC* kann in die häufiger vorkommende *extramedullären Form* – oft in Kombination mit einer subarachnoidalen kranialen NCC [38] – sowie in die seltenere *intramedulläre Form* unterteilt werden [39]. Auch können beide Formen gemeinsam vorkommen [40]. Bei der extramedullären Form wurden unter anderem eine progressive Schwäche der unteren Extremitäten, Stuhl- und Urininkontinenz sowie Rückenschmerzen als vorrangige Symptome beschrieben [40–42], bei der intramedullären Form eine partielle oder vollständige transverse Myelopathie, welche durch eine motorische Schwäche in der Höhe der Läsion und eventuelle Spastik unterhalb der Läsion, partielle oder vollständige Sensibilitätsausfälle unterhalb der Läsion sowie Harn- und Stuhlinkontinenz bzw. -verhalt charakterisiert ist. Auch bei der intramedullären Form werden Rückenschmerzen als spezifische Symptome beschrieben [39].

Zu der häufigsten Manifestation der Zystizerkose außerhalb des Zentralnervensystems zählt die *okuläre Zystizerkose.* Von dieser sind vor allem Kinder und junge Erwachsene betroffen [43]. Hier siedeln sich einzelne *T. solium* Zystizerken im Glaskörper, seltener im retinalen oder subretinalen Bereich an. Insbesondere beim Absterben des Parasiten kann es dann zu einer massiven Entzündungsreaktion mit schweren Reaktionen in der vorderen Augenkammer, retinalen Einblutungen bis hin zur Ablösung oder einem sekundären Glaukom kommen [44]. Aus Indien wird häufiger auch von einer Manifestation der Zystizerken in der okulären Adnexe berichtet (*orbitale/adnexale Zystizerkose*) [44]. Einer retrospektiven Studie von 166 Fällen in Indien zufolge waren die häufigsten Symptome bei der Vorstellung dieser Patienten eine periokuläre Schwellung (38 %), Proptosis (24 %) oder Ptosis (14 %) [43].

Liegen *T. solium* Zystizerken nicht oder nicht ausschließlich im Gehirn, dem Rückenmark oder dem Auge, sondern im subkutanen oder muskulären Bindegewebe vor, spricht man von einer *systemischen/dissiminierten Zystizerkose* [7]. Diese kann wiederum nach der genauen Lokalisation der Zystizerken unterteilt werden: Eine *subkutane Zystizerkose* wurde bisher vor allem bei

Patienten mit Herkunftsländern in Asien, vereinzelt jedoch auch in Lateinamerika oder dem südlichen Afrika beschrieben. Diese Ausprägung präsentiert sich mit vereinzelten oder zahlreichen abgrenzbaren subkutanen Knoten, die eine Größe bis zu 4 cm erreichen können [45, 46]. Im Weiteren können sich Zystizerken – oft auch sehr zahlreich – in der Skelettmuskulatur der Extremitäten und des Rumpfes sowie der Zungen- oder Kaumuskulatur ansiedeln (*muskuläre Zystizerkose*) [47, 48]. Dies kann bei hochgradiger Ausprägung schmerzhafte Muskelverhärtungen/-schwellungen und damit verbunden funktionellen Einschränkungen zur Folge haben. Eine Manifestation im Herzmuskel (*kardiale Zystizerkose*) ist selten und kann klinisch symptomfrei verlaufen, eventuell aber auch zu Veränderungen im Elektrokardiogramm (abnorme P- und T-Wellen) bis hin zum Herzversagen führen [49].

Träger des adulten Wurms im Darm weisen meist keine klinische Symptomatik auf [50, 51]. Unspezifische Symptome wie z. B. Magenschmerzen, Durchfall, Übelkeit, Ausbildung eines Blähbauchs, Kopfschmerzen und Depression sind zwar beschrieben, wurden bisher aber nicht systematisch nachgewiesen [31, 50, 51]. Die häufige Abwesenheit von Symptomen stellt für die Prävention und Kontrolle der TSCT eine besondere Herausforderung dar, da Träger des adulten Wurms oft unbemerkt bleiben und so eine persistierende Infektionsquelle darstellen.

1.4 Diagnose der *T. solium* Neuro-/zystizerkose und Täniose

Die Diagnose der NCC beruht auf einer zielgerichteten Anamnese (mit Fragen zum Herkunftsland, Reisen in endemische Länder sowie dem Konsum von Schweinefleisch) sowie einer klinisch-neurologischen Untersuchung mit neuroradiologischen und labordiagnostischen Folgeuntersuchungen. Den Goldstandard in der NCC-Diagnostik stellt die neuroradiologische Untersuchung mittels Computer (CT)- und/oder Magnetresonanztomografie (MRT) dar. Die CT- und/oder MRT-Untersuchung dient neben der eigentlichen Diagnose auch der prognostischen Beurteilung einer vorliegenden NCC für die Wahl der Therapie sowie dem nachfolgenden Therapiemonitoring. Serologische Untersuchungen (Zystizerkose-Ag und -Ak) werden vor allem für die Bestätigung, aber auch für die Erfolgseinschätzung (v. a. mittels Zystizerkose-Ag-Titern) einer medikamentösen Therapie herangezogen [1, 36]. Im *Liquor cerebrospinalis* sind meist nur unspezifische Veränderungen zu finden, eine Eosinophilie ist selten [7]. Auch hier können beim Vorliegen einer NCC spezifische *T. solium*-Ag und -Ak gemessen werden. Wegen ihres invasiven Charakters hat diese Untersuchung jedoch nur eine untergeordnete Bedeutung in endemischen Ländern.

Im Jahr 2017 veröffentlichten die Infectious Diseases Society of America (IDSA) zusammen mit der American Society of Tropical Medicine and Hygiene (ASTMH) erste Richtlinien für die Diagnose und Behandlung der NCC [52]. Diese Richtlinien wurden vor allem für den nordamerikanischen Raum sowie generell strukturstarke Länder entwickelt. Darin empfohlene neuroradiologische sowie labordiagnostische Untersuchungsmethoden stehen in endemischen Ländern häufig nicht oder nicht in ausreichendem Umfang zur Verfügung [1]. Diesem Umstand wird in den derzeit von der WHO und einem Expertengremium zusätzlich entwickelten Richtlinien für die Diagnose und Therapie der NCC in strukturschwachen Ländern Rechnung getragen. Dabei wird ein verstärktes Augenmerk auf eine rein laborbasierte Diagnostik beim Fehlen von neuroradiologischen Untersuchungsmethoden sowie auf die Diagnostik der eng verbundenen Täniose gelegt. Die Richtlinien der WHO werden voraussichtlich Mitte 2021 veröffentlicht (pers. Kommunikation mit Dr. Abela-Ridder, Leitung des Department for the Control of Neglected Tropical Diseases der WHO, Genf).

Das Vorliegen einer NCC sowie deren Unterteilung in eine wahrscheinliche oder eine definitive NCC (dies inkludiert in diesem Kontext auch eine *okulärere Zystizerkose*) kann mittels des von Del Brutto und Kollegen im Jahr 2017 optimierten Diagnoseschemas durchgeführt werden [53]. Dieses Schema basiert auf der Definition von absoluten (wie einem histopathologisch oder funduskopisch eindeutigen Nachweis des Parasiten), neuroradiologischen sowie klinisch spezifischen Kriterien (wie z. B. einem Nachweis von Zystizerkose-Ak und/oder -Ag mit gut validierten Labortests, dem nachgewiesenen Kontakt mit einem im selben Haushalt lebenden Täniose-Patienten, der Herkunft aus einem endemischem Gebiet), welche jeweils unterschiedlich gewichtet werden („minor/major criteria“) [53].

Für die serologiebasierte Zystizerkose-Diagnose stehen vor allem der Nachweis von für *T. solium* spezifischen Ak (vorrangig IgG) und Ag in Serum (oder *Liquor cerebrospinalis*) im Vordergrund.

Eine Vielzahl von Labortests wurde entwickelt, nur wenige davon sind bisher jedoch ausreichend validiert und/oder kommerziell erhältlich [55–56]. Der Nachweis von Zystizerksoe-Ak findet nicht nur in der individuellen Patientendiagnostik, sondern auch in epidemiologischen Studien Anwendung und wird ebenfalls zumeist mittels nicht kommerzieller Tests durchgeführt [56]. Zur Anwendung kommen vorrangig Immunoblot-Assays oder weniger sensitive und spezifische ELISA-Tests. Das Ak-detektierende Agens sind hier vor allem aufgereinigte Zystizerkenextrakte (häufig Zystizerkenflüssigkeit), Glykoproteinfraktionen oder rekombinante Ag (z. B. rT24H) [55, 56]. Der Test mit der höchsten Sensitivität (96 % bei Vorliegen von mehr als einem kranialen Zystizerkus) und Spezifität (97 %) ist hier der an den Centers for Disease Control and Prevention (CDC) Atlanta von Tsang et al. entwickelte Lentil-Lectin aufgereinigter Glykoprotein (LLGP-) EITB, welcher aus sieben geblotteten Lentil-Lectin aufgereinigten Glykoproteinfraktionen besteht [57] (Abbildung 10). Der LLGP-EITB gilt derzeit als Goldstandard-Test für die serologische Bestätigung einer NCC, benötigt jedoch kostspieliges Equipment für die Herstellung des Glykoproteinfraktionsextrakts. Es sind auch kommerzielle Varianten dieses LLGP-Protokolls (z. B. von der Firma LDBIO, Lyon, Frankreich: Cysticercosis WB IgG mit einer Sensitivität von 97,5 % und spezifiziert von 100 % laut Hersteller) auf dem Markt. Auch diese kommerziellen LLGP-EITB-Tests sind kostspielig und bleiben deshalb nur wenigen Laboren mit ausreichend finanziellen Mitteln vorbehalten. Eine klinische Studie, die in 60 Dörfern in Burkina Faso durchgeführt wurde, wies kürzlich den ebenfalls am CDC Atlanta entwickelten und auf dem rekombinanten Protein rT24H basierenden Immunoblot [58, 59] im direkten Vergleich mit dem LLGP-EITB als fast gleichwertige Alternative nach (Übereinstimmung beider Tests: kappa value = 0,89) [60] (Abbildung 10). Auch dieser Test ist derzeit nur als In-house-Assay verfügbar, jedoch in der Herstellung deutlich einfacher und kostengünstiger [58, 61].

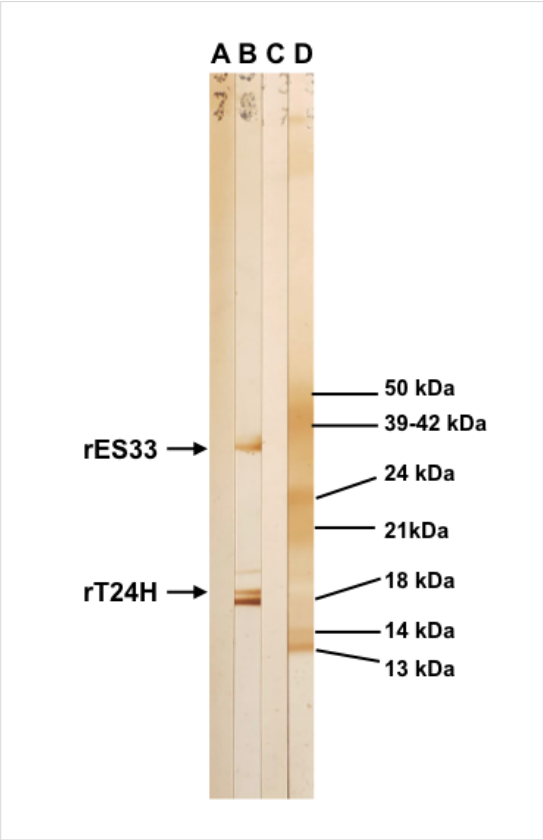

Abbildung 10. rES33/rT24H-Immunoblot (B) und LLGP-EITB (D) inkubiert mit negativen (A, C) und positiven (B, D) NCC Seren. (Test-Herstellung und Durchführung sowie Bild: Veronika Schmidt)

Der *T. solium* Ag-Nachweis, der vor allem zum Nachweis einer aktiven NCC sowie für das Monitoring während der Therapieanwendungen herangezogen wird, erfolgt meist mithilfe von ELISA-Tests. Hier sind vor allem zwei Assays routinemäßig im Einsatz: der monoklonale B158/B60 Ag-ELISA, der eine laborbasierte Sensitivität von 90 % und eine Spezifität von 98 % aufweist [62], sowie der HP10 Ag-ELISA, der vor allem für extraparenchymatöse NCC sowie die Testung von *Liquor cerebrospinalis* von Bedeutung ist [63, 64]. Der B158/B60 Ag-ELISA wurde von der Firma ApDIA (Turnhout, Belgien) kommerzialisiert, ist jedoch wiederum relativ kostenintensiv für Einzeltestungen und deshalb eher für epidemiologische Studien und Laboratorien mit ausreichenden Mitteln geeignet. Beide Ag-ELISA-Tests basieren ursprünglich auf der Detektion von *T. saginata*-Ag und es kommt deshalb zu Kreuzreaktionen [56].

Bei der Diagnose der *okulären Zystizerkose* stehen die Funduskopie sowie ultrasonografische Untersuchungsmethoden im Vordergrund [43, 44], bei der *systematischen Zystizerkose* die Biopsie, histopathologische Untersuchungen, Röntgenuntersuchungen, chungen sowie molekulare Tests [45, 40, 56].

Der Nachweis einer intestinalen Infektion mit einem adulten Wurm *T. solium* erfolgt makroskopisch (Proglottiden im Stuhl werden meist als reisförmig oder bandnudelartig beschrieben) sowie mikroskopisch (Nachweis der speziesspezifischen sieben bis zwölf Uterusäste in graviden Proglottiden mittels gefärbtem Quetschpräparat bzw. Nachweis der intermittierend ausgeschiedenen Eier von *T. solium* mittels Kato-Katz-Methode im Stuhl) [7, 50, 56]. Der mikroskopische Nachweis von Eiern weist nur eine sehr geringe Sensitivität auf (3,9 % bis 52,5 %) [56]. Dieser Nachweis

erfordert mindestens drei Stuhlproben von drei verschiedenen Tagen und erlaubt keine Speziesspezifizierung zwischen *T. solium, T. saginata* und *T. asiatica*. Von Guezala et al. wurde ein speziesspezifischer Kopro-Ag-ELISA Test entwickelt, welcher jedoch nur vereinzelt im Rahmen von Forschungsprojekten zur Verfügung steht [65]. Der molekulare Nachweis mittels klassischer oder Real-Time-PCR-Protokolle (wie das von der WHO derzeit empfohlene Nested-PCR-Protokoll von Mayta et al. [66]) von *T. solium*-DNA in Stuhlproben ist die sensitivste und spezifischste Nachweismethode einer adulten Wurminfektion [67]. Vor allem für epidemiologische Studien steht darüber hinaus der serumbasierte Nachweis von *T. solium*-Täniose-Ak (mittels rekombinanter exkretorisch-sekretorischer rES33- und rES38- Antigene) mit Immunoblots zur Verfügung [68, 69]. Serologische und molekularbiologische Täniose-Tests sind durchwegs In-house-Tests, kaum validiert und nicht kommerziell erhältlich.

Bedeutsam für die Diagnose der TSCT in endemischen Ländern ist, dass die derzeit empfohlenen Labortests meist nicht vor Ort verfügbar sind oder die dafür erforderlichen finanziellen Mittel fehlen. Besonders in strukturschwachen Ländern – wie Tansania – stehen deshalb außerhalb von Forschungsprojekten meist keine serologische Diagnostik für TSCT und nur wenige CT-Apparate (< 10) für eine radiologische NCC-Diagnostik zur Verfügung. Aus diesem Grund wird derzeit intensiv an neuen kostengünstigeren Testformaten (wie magnetischen Immunografie-Tests [70], Quick ELISA^{TM} [71], Lateral Flow Assays [72, 73], Objektträger-Agglutinationstests [74] für die serologische Detektion von Zystizerkose oder Loop mediated-PCRs [75] für die koprologische Detektion einer Täniose) gearbeitet. Diese Tests befinden sind allerdings erst in der Entwick-lungsphase oder sind für einen Routineeinsatz noch nicht ausreichend validiert. Außerdem be-nötigen einige dieser Testkandidaten Lesegeräte oder spezielle Reagenzien, die eine Anwen-dung in strukturschwachen Gebieten wiederum einschränken könnte. Um eine weitere zielgerich-tete Entwicklung neuer kostengünstiger Expertentreffen in Genf statt, bei dem genaue Zielproduktprofile für Forschungseinrichtungen und die Industrie definiert wurden [76, 77].

1.5 Therapie und Prognose der *T. solium* Neuro-/zystizerkose und Täniose

Für die Behandlung der NCC stehen derzeit die Richtlinien für die Diagnose und Behandlung der NCC der IDSA und ASTMH zur Verfügung [52]. Darüber hinaus wurden zahlreiche Therapieregime veröffentlicht. Deren allgemein gültige Aussagekraft ist jedoch häufig durch eine geringe Anzahl an Studienteilnehmer und/oder das Fehlen eines systematischen Studiendesigns limitiert [1]. Generell zeigt sich, dass die Behandlung der NCC individualisiert erfolgen muss [7]. Im Allgemeinen richtet sich die Therapie stark nach dem individuellen klinischen Erscheinungsbild, im Speziellen nach dem Vorliegen (aktive NCC) oder Fehlen (inaktive NCC) von aktiven Zystizerken im Gehirn, deren Anzahl, Lokalisation sowie dem Vorhandensein weiterer pathologischer Veränderungen wie einem entzündlichen Ödem und/oder einem erhöhten Hirndruck. Es besteht Einigkeit darüber, dass Patienten mit einer inaktiven NNC ohne spezifische Symptome nicht medikamentös behandelt werden sollten [1, 7, 36]. Eine entsprechende Aufklärung über das mögliche Auftreten von Symptomen zu einem späteren Zeitpunkt scheint jedoch sinnvoll. Im Falle einer inaktiven NCC mit bereits bestehender Symptomatik (meist epileptische Anfälle) ist vorrangig eine rein symptomatische Behandlung einzuleiten [1, 36]. Diese besteht in strukturschwachen Ländern bei epileptischen Anfällen aus einer antikonvulsiven Therapie mit Phenobarbiton, Phenytoin und Carbamazepine (je nach Verfügbarkeit). Den Richtlinien der International League

Against Epilepsy (ILAE) zufolge sollte beim Vorliegen einer NCC-verdächtigen Läsion im CT bereits nach dem ersten Anfall mit einer antikonvulsiven Medikation begonnen werden [1, 78]. Liegt eine aktive NCC vor, sollte zusätzlich eine anthelminithische Therapie in Betracht gezogen werden. Bei den spezifischen Anthelminithika liegen für Praziquantel (50 mg/kg x3/d über zwei Wochen bis zu einem Monat) die meisten Daten vor [1, 7]. Praziquantel ist auch in einem Großteil der endemischen Länder gut erhältlich. Albendazol (15 mg/kg x2/d über ein bis zwei Wochen) wird empfohlen, ist in strukturschwachen Ländern jedoch deutlich schwerer oder gar nicht erhältlich und deshalb vor allem in strukturreichen Ländern von Bedeutung [1, 7]. In einer kontrollierten Vergleichsstudie wurde auch der positive Effekt einer Kombination beider Anthelmithika beschrieben [79]. Das Ziel einer anthelminthischen Therapie sind die Degeneration und im idealen Fall die Auflösung der Zystizerken. Durch das dabei mögliche Auftreten massiver lokaler immunologischer Reaktionen birgt die anthelminthische Therapie jedoch das Risiko einer Exazerbation der Symptomatik (wie eines starken Anstiegs der Frequenz epileptischer Anfälle) und kann deshalb nicht als Standardtherapie gesehen werden. Im Falle einer anthelminthischen Therapie ist in den meisten Fällen die zusätzliche Gabe von Kortikosteroiden indiziert und eine Hospitalisierung in Erwägung zu ziehen [1, 7]. Eine Exazerbation unter Therapie muss vor allem beim Vorliegen einer *subarachnoidalen NCC* sowie beim Vorliegen multipler intraparenchymatöser Zystizerken mit entzündlichem Ödem in Betracht gezogen werden. Derzeit gibt es keine Standardtherapie mit Kortiksoteroiden. Meist kommen Prednisolon (1 mg/kg x1/d p. o oder i. v.) oder Dexamethason (6 bis 8 mg bis maximal 30 mg x1/d p. o. oder i. v.) zum Einsatz, welche häufig über einen längeren Zeitraum verabreicht werden müssen [1, 7]. In Einzelfällen kann eine symptomatische Therapie auch ausschließlich mit Kortikosteroiden unterstützt werden [1]. Sofern keine CT-/MRT-Untersuchung möglich ist – wie dies häufig in strukturschwachen Gebieten der Fall ist – und eine Diagnose nur auf der klinischen Symptomatik verbunden mit oder ohne serologischen Ergebnissen aufgebaut werden kann, wird von einer anthelminthischen Therapie abgeraten. Hier wird eine rein symptomatische Therapie mit Antikonvulsiva, Analgetika und/oder Steroiden empfohlen [1]. Bei intraventrikulären Zystizerken steht eine neuroendoskopische Entfernung im Vordergrund [7]. Das Legen eines ventrikuloperitonealen Shunts kann vor allem beim Vorliegen eines Hydrozephalus erforderlich sein. Bei der *okulären Zystizerkose* wird ausschließlich eine operative Entfernung von Zystizerken empfohlen, da eine medikamentöse Therapie zu irreversiblen Schäden führen kann [7]. Zu beachten ist auch, dass solche invasiven Eingriffe in strukturschwachen Ländern aus Mangel an qualifiziertem Personal oft nicht durchgeführt werden können und für den Patienten durch beschränkte Mittel, mangelhafte Hygienebedingungen sowie eine häufig lückenhafte Nachsorge in vielen Gesundheitseinrichtungen erhebliche Risiken bergen können [1]. Prognostisch ist eine aktive parenchymatöse NCC deutlich besser als eine extraparenchymatöse NCC einzuschätzen [1].

Bei der Therapie einer Täniose sind Praziquantel (5 bis 10 mg/kg Einmalgabe) und Niclosamid (2 g Einmalgabe) derzeit die Mittel der Wahl [7, 50, 80, 81]. Aber auch eine Dreifachdosis von Albendazol (3 x 400 mg an drei aufeinanderfolgenden Tagen) zeigte eine hohe Erfolgsrate [51, 82]. Praziquantel ist hierbei die am öftesten verfügbare und günstigste Medikation (0.05 bis 0.1 $/Patient) im Gegensatz zu Niclosamid für ~5 $/Patient [50, 82, 84]. Dies ist insbesondere für strukturschwache Länder von Bedeutung. Da Praziquantel – im Gegensatz zu Niclosamid – jedoch die Blut-Hirn-Schranke durchdringen kann, bestehen hier Bedenken im Kontext mit einer möglichen Aktivierung einer latenten NCC [50, 80]. Für Praziquantel liegt ein Therapieerfolg bei 95 % und für Niclosamid bei 85 % [1, 50].

Über die Elimination des adulten Wurms im Darm und damit potentiell verbundene Symptome hinaus hat die effiziente Täniose-Chemotherapie große Bedeutung in der Vorbeugung einer Autoinfektion des Patienten mit Eiern von *T. solium* und somit einer Ausbildung einer Neuro-/zystizerkose. Außerdem ist eine Täniose-Massentherapie (MDA) (z.B. bei Schulkindern) für die Prävention einer Ausbreitung von *T. solium* von großer Wichtigkeit [30, 85].

In Tansania wird bisher aus Ermangelung entsprechender Fachkenntnisse des ärztlichen Personals sowie entsprechender radiologischer und serologischer Diagnosemöglichkeiten nicht auf TSCT untersucht. Es sind auch keine nationalen Therapierichtlinien vorhanden (pers. Kommunikation mit Dr. Bernard Ngowi, National Institute for Medical Research [NIMR], Dar es Salaam, Tansania).

1.6 Prophylaxe, Prävention und Kontrolle von *T. solium*

Für die individuelle Prophylaxe einer Infektion mit *T. solium* wurden zahlreiche Empfehlungen formuliert [1, 7, 50]: Um einer NCC vorzubeugen, ist das Waschen der Hände mit Seifenwasser nach dem Toilettengang, nach dem Wechseln von Windeln und vor der Zubereitung von Essen von großer Wichtigkeit [7]. Darüber hinaus wird das sorgfältige Waschen und Schälen von Früchten und Gemüse empfohlen. Während Auslandsreisen in endemische Gebiete soll auf sichere Wasser- (gefiltertes Wasser oder abgefülltes Wasser) und Lebensmittelquellen (das Meiden von Straßenküchen oder sog. „local bars“) geachtet werden [86]. Die wichtigsten Prophylaxemaßnahme zur Vermeidung einer Täniose besteht in der Vermeidung des Konsums von rohem oder halbrohem Schweinefleisch [8]. Nur Einfrieren von infestiertem Fleisch über mindestens vier Tage bei -5°C, drei Tage bei -15°C oder einen Tag bei -24°C tötet Zystizerken wirkungsvoll ab [50, 87].

In strukturschwachen Gebieten können diese Prophylaxemaßnahmen durch Wasser- und Lebensmittelknappheit, Mangel an sauberen Wasserquellen sowie kulturelle Hindernisse häufig nicht adäquat durchgeführt werden. Für die Fleischbeschau von Schweinefleisch in einkommensschwachen Ländern entwickelte die Food and Agriculture Organization der Vereinten Nationen (FAO) ein Handbuch, in dem jedoch nur sehr kurz auf *T. solium* eingegangen wird [88].

Für eine großflächige Prävention, Kontrolle und mögliche Elimination von *T. solium* in endemischen Gebieten müssen sowohl der Hauptwirt Schwein als auch der Mensch in Interventionen mit einbezogen werden. Dies verlangt eine enge multidisziplinäre Zusammenarbeit des Medizin-, Veterinär-, Sozial- und Bildungssektors. Verschiedene Kontrollprogramme sind derzeit in Erprobung und deren Langzeiteffekt sowie die Kombination unterschiedlicher Strategien wir untersucht [1, 83, 84, 89]:

- Breitflächige Massenchemotherapie (MDA)-Programme (z. T. integriert in Präventionsprogramme für andere parasitäre Erkrankungen wie z. B. Schistosomiasis, Onchozerkose)
- Behandlung von Täniose-Patienten [90]
- Verstärkte Bildungsinterventionen in relevanter Kohorten (z. B. Schulkinder [26])
- Verbesserung von Hygienebedingungen (z. B. durch den Bau von Latrinen und sicheren Brunnenanlagen)
- Verbesserte Schweinehaltungssysteme
- Anthelminthische Therapie und Vakzinierung von Schweinen
- Verbesserung der Fleischinspektion und Verarbeitung von Fleischprodukten

Im Jahr 1993 wurde die Infektion mit *T. solium* von der Task Force for Disease Eradication der CDC als potenziell eliminierbar eingestuft [91]. Ob und wann dieses Ziel erreicht werden kann, bleibt jedoch fraglich, da zur Erreichung enorme finanzielle Mittel erforderlich sind, kulturelle Hindernisse (z. B. Tabus in der Körperhygiene und der Schweinehaltung) überwunden und Interventionen – in teils politisch instabilen Ländern – über einen langen Zeitraum konsequent durchgeführt werden müssen.

1.7 *T. solium* Neuro-/zystizerkose und Täniose in speziellen Kohorten

Bei den epidemiologischen Untersuchungen von *T. solium* sind allgemeine Querschnittstudien im ländlichen Bereich sowie krankenhausbasierte Studien von Epilepsiekohorten die häufigsten Rekrutierungsansätze. Durch die zunehmenden Bestrebungen, strukturangepasste Behandlungsrichtlinien sowie kulturell angepasste Präventions- und Kontrollprogramme zu entwickeln, wird nun aber auch den Aspekten von TSCT in speziellen Kohorten (wie besonderen demografischen Kohorten) und den damit einhergehenden Besonderheiten immer mehr Interesse geschenkt [1]. Entsprechend können sich daraus auch Konsequenzen für die spezielle Anwendung von Diagnostika und Therapeutika ergeben [91].

Ein Beispiel hierfür stellt die Gruppe von Kindern und Jugendlichen dar. Hier wird unter anderem die Notwendigkeit des Einsatzes von Anthelminthika in der NCC Therapie diskutiert, da vereinzelte kolloidale parenchymatöse Zystizerken – mit guter Prognose – deutlich häufiger bei Kindern zu finden sind und es zusätzlich öfter zu spontanen Resolutionen der Zystizerken kommt. Dies würde gegen die Inkaufnahme potenzieller Risiken, die mit einer anthelminthischen Therapie sowie der Einnahme von Kortikosteroiden verbunden sein können, und – im Gegensatz zu Erwachsenen – für eine rein symptomatische Therapie sprechen [1, 92–95]. Auch bei der Therapie mit Antikonvulsiva sind wahrscheinlich Besonderheiten bei Kindern mit NCC zu beachten (z. B. eine verlängerte Therapiedauer und eine häufiger notwendige Kombination von Medikamenten) [1, 95].

Im Weiteren können sich bei der genaueren Betrachtung geografisch unterschiedlicher Kohorten – wie z. B. urbaner versus ländlicher Kohorten – Abweichungen bei den Infektionswegen und somit erforderlich Anpassungen bei Präventionsmaßnahmen ergeben [96], wie dies bereits für andere parasitäre Infektionskrankheiten – wie lymphatische Filariose und Malaria – bekannt ist [97, 98]. Auf mehr Hintergrundinformation dazu wird in der Veröffentlichung im Anhang I eingegangen.

Eine weitere spezielle Kohorte, für die bisher zu wenige Daten im Zusammenhang mit *T. solium* vorliegen, stellen Patientengruppen mit Co-Infektionen dar: Die globale Forschung zur Verbreitung und zu speziellen klinischen Aspekten der TSCT ist relativ jung. Obwohl bereits 1558 der erste NCC-Fall in der Literatur beschrieben wurde und seit 1970 mit der Erfindung des CTs die dokumentierten NCC-Fälle deutlich angestiegen sind, wurden vorwiegend Fallbeschreibungen und epidemiologische Daten aus einigen wenigen Ländern wie Peru, Mexiko und den USA veröffentlicht [99]. Im vergangenen Jahrzehnt stiegen die internationalen Bemühungen an, auf diese vernachlässigte Infektionskrankheit auch auf anderen Kontinenten mehr Augenmerk zu legen. Hierbei wurde rasch deutlich, dass viele Länder, in denen *T. solium* endemisch ist, auch Hochendemiegebiete für andere Infektionskrankheiten – wie HIV/AIDS, Tuberkulose und Malaria – darstellen. Es wird angenommen, dass in einigen Entwicklungsländern bis zu einem Drittel der

Bevölkerung von diesen Erkrankungen betroffen ist [100]. Die Bedeutung von Co-Infektionen mit Parasiten (z. B. HIV/AIDS – Malaria, HIV/AIDS – vom Boden übertragene Helminthen) wird in diesem Zusammenhang u.a. mit der Empfänglichkeit für Neuinfektionen sowie der Pathogenese und Sensitivität von Diagnostika zunehmend diskutiert [100–103]. Für Co-Infektionen mit *T. solium* liegen hierzu noch kaum Daten vor. Aus diesem Grund wurde ein Teil der vorliegenden Dissertation dieser Fragestellung gewidmet und weitere Details zu Aspekten von TSCT und Co-Infektionen sind in der Veröffentlichung im Anhang II ausführlicher dargestellt.

2 Fragestellungen und Zielsetzung der Dissertationsarbeit

Das Ziel dieser Dissertation war die Untersuchung von Aspekten der TSCT in zwei speziellen Kohorten in Tansania: 1. in einer Epilepsiekohorte im peri-/urbanen Bereich (Dar es Salaam) und 2. in einer mit HIV co-infizierten Kohorte in Nord-Tansania. Für beide Kohorten sind bisher noch keine oder kaum Daten verfügbar und zahlreiche epidemiologische sowie klinische Fragen dazu sind offen.

Die übergeordnete Fragestellung im Zusammenhang mit TSCT in einem peri-/urbanen Gebiet lautete (s. Veröffentlichung I) lauetete:

- Spielt *T. solium* als Erreger für Epilepsiepatienten in einem peri-/urbanen Gebiet eines endemischen Landes in Subsahara Afrika – am Beispiel Tansania und Dar es Salaam – eine ursächliche Rolle?

Die speziellen Fragestellungen dazu lauteten:

1. Wie hoch ist die Prävalenz von NCC in einer Epilepsiekohorte in Dar es Salaam?
2. Gibt es Hinweise auf klinisch-radiologische Unterschiede von Patienten mit NCC im Vergleich zu vergleichbaren Daten aus dem ländlichen Bereich?
3. Wie hoch ist die Ak-Seroprävalenz der *T. solium* Täniose in dieser speziellen Kohorte?
4. Gibt es Hinweise auf demografische Unterschiede (wie z. B. Alter, Geschlecht, Beruf) von Patienten mit TSCT in dieser Kohorte zu vergleichbaren Daten aus dem ländlichen Bereich? Wenn ja, worin bestehen diese Unterschiede?

Die übergeordnete Fragestellung im Zusammenhang mit TSCT im Kontext einer HIV-Co-Infektion lautete (s. Veröffentlichung II) lautete:

- Welche epidemiologische und klinische Bedeutung hat eine Co-Endemie/-Infektion von TSCT mit HIV – am Beispiel einer bekannt co-endemischen Kohorte in Nord-Tansania?

Die speziellen Fragestellungen dazu lauteten:

1. Wie hoch ist die Prävalenz von NCC in einer Gruppe von HIV-co-infizierten Patienten im Vergleich zu einer HIV-negativen Kontrollgruppe?
2. Gibt es Hinweise auf klinisch-radiologische Unterschiede von Patienten mit NCC in den beiden Gruppen?
3. Wie hoch ist die Ak-Seroprävalenz der *T. solium* Täniose in den beiden Gruppen?
4. Gibt es Hinweise auf demografische Unterschiede (wie z. B. Alter, Geschlecht, Beruf) von Patienten mit TSCT in den beiden Gruppen? Wenn ja, worin bestehen diese Unterschiede?

Zur Beantwortung dieser Fragestellungen wurden mehrjährige Studien in Dar es Salaam und in Nord-Tansania durchgeführt und von der Doktorandin mit betreut.

3 Kurzdarstellung der Veröffentlichungen und des Eigenanteils

Im Folgenden werden der Inhalt und der Beitrag der Doktorandin an den beiden Studien und den beiden Veröffentlichungen im Einzelnen genauer dargelegt:

3.1 Veröffentlichung I: „*Taenia solium* cysticercosis and taeniasis in urban settings: Epidemiological evidence from a health center-based study among people with epilepsy in Dar es Salaam, Tanzania“

Hintergrund:

Die Bevölkerungszahlen in afrikanischen Städten und damit die Ausdehnung urbaner Gebiete steigen rapide an. Dies bringt völlig neue Aspekte für die Übertragung von Infektionskrankheiten mit sich, wie dies bereits von anderen Erregern (z. B. *Plasmodium ssp.* und *Mycobacterium tuberculosis)* bekannt ist. Der Zoonoseerreger *T. solium* stellt eine bedeutende Ursache für erworbene Epilepsie in endemischen Gebieten dar. Für ländliche Gebiete in Subsahara-Afrika liegen hierzu bereits einige Daten vor, jedoch nicht für peri-/urbane Gebiete.

Methoden:

In dieser Studie wurden insgesamt 302 Patienten mit Epilepsie in sechs Gesundheitszentren des Kinondoni-Distrikts von Dar es Salaam, Tansania, rekrutiert. Alle Studienteilnehmer wurden klinisch sowie mittels CT-Untersuchungen (mit und ohne Kontrastmittel) untersucht. Außerdem wurden Ag- und Ak-Titer für *T. solium* Zystizerkose sowie Täniose mittels Immunoblot und ELISA-Tests am CDC Atlanta getestet. Bei positiven Patienten wurden weitere serologische und radiologische Folgeuntersuchungen vorgenommen. Demografische Daten wurden mittels Fragebogen erhoben und potenzielle Risikofaktoren, die mit *T. solium* Infektionen assoziiert sind, untersucht.

Ergebnisse:

T. solium Zystizerkose-Ag wurde in drei (0,99 %; 95 % CI: 0–2,11 %), -Ak in acht (2,65 %; 95 % CI: 0,84–4,46 %) und Täniose-Ak in fünf (1,66 %; 95 % CI: 0,22–3,09 %) der 302 Patienten mit Epilepsie detektiert. Sechs Patienten (1,99 %; 95 % CI: 0,41–3,56 %) wurden mit NCC diagnostiziert. Mit *T. solium* infizierte Patienten berichteten signifikant häufiger von fokalen Anfällen sowie dem Auftreten einer Aura ($p < 0.01$ und $p = 0.03$).

Schlussfolgerung:

Es konnte zwar nachgewiesen werden, dass *T. solium* im Zusammenhang mit Epilepsie auch im peri-/urbanen Bereich ursächlich eine Rolle spielen kann, jedoch wurde eine deutlich niedrigere Prävalenz der Infektion im Vergleich zu ländlichen Gebieten gefunden. Dies spricht gegen eine verbreitete aktive Übertragung von *T. solium*. Die geringe Anzahl an mit *T. solium* infizierten Patienten ließ darüber hinaus keine profunde Schlussfolgerung über spezielle Risikofaktoren für den peri-/urbanen Bereich zu.

Eigenanteil:

In dieser Studie hat die Doktorandin das Studienteam angeleitet und immer wieder vor Ort unterstützt sowie erforderliche Studienunterlagen (wie z. B. Standardarbeitsanweisungen) entwickelt. Im Weiteren organisierte sie den gesamten labordiagnostischen Arm dieser Studie ab der Blutabnahme inkl. Transport und nahm die Testung aller Proben mit zwei In-house-Immunoblots (LLGP-EITB und rT24H/rES33-Immunoblot) sowie dem B158/B60 Ag-ELISA am CDC Atlanta vor. Die Doktorandin führte alle Daten in einer Datenbank zusammen und wertete diese zusammen mit Prof. Dr. Herbinger aus. Abschließend wurde die entsprechende Veröffentlichung von der Doktorandin als Erstautorin verfasst.

3.2 Veröffentlichung II: „Association between *Taenia solium* infection and HIV/AIDS in northern Tanzania: a matched cross-sectional study“

Hintergrund:

In vielen Ländern Subsahara-Afrikas steigt das Vorkommen des zoonotischen Bandwurms, *T. solium*, bei Mensch und Schwein an. In denselben Verbreitungsgebieten herrscht eine hohe Prävalenz des HI-Virus vor. Bisher ist kaum bekannt, ob und wie diese beiden Erreger im menschlichen Körper interagieren und ob eine Immunsuppression bei der Entstehung und Ausprägung von NCC von Bedeutung ist. Das Ziel dieser Studie war, die Häufigkeit und Ausprägung der TSCT erstmals in einer HIV-positiven Gruppe und einer HIV-negativen Kontrollgruppe zu ermitteln sowie die Ergebnisse zu vergleichen und daraus erste mögliche Schlüsse auf die Bedeutung dieser Co-Infektion zu ziehen.

Methoden:

In Nord-Tansania wurden 170 HIV-positive Patienten in einem Krankenhaus (Abbildung 11) und 170 HIV-negative Kontrollindividuen in umliegenden Distrikten (Abbildung 12) – jeweils nach Geschlecht, Alter und Ort abgeglichen – rekrutiert und anschließend untersucht. Es wurde eine Klassifizierung der HIV-Infektionen vorgenommen und bei allen Studienteilneh-mern wurden serologische Tests auf *T. solium*-Ag und -Ak durchgeführt. Neurologische Symp-tome/ pathologische Zeichen wurden mittels einer neurologischen Standarduntersuchung ermit-telt und die Diagnose einer NCC wurde mittels zusätzlicher CT-Untersuchungen unter der Verwendung von Standardkriterien gestellt. Darüber hinaus wurden demografische und klinische Da-ten in beiden Studiengruppen erhoben. Bei HIV-positiven Patienten wurden außerdem CD4+-Zellzahl-Ergebnisse sowie Informationen zur antiretroviralen Therapie (HAART) gesammelt.

Ergebnisse:

In dieser Studie konnten keine signifikanten Unterschiede in der Seroprävalenz von Täniose-Ak (0.6 % vs. 1.2 %), Zystizerkose-Ak (2.4 % vs. 2.4 %) sowie Zystizerkose-Ag (0.6 % vs. 0.0 %) zwischen der Gruppe der HIV-positiven Patienten sowie der HIV-negativen Kontrollgruppe gefun-den werden. Insgesamt wurden sechs NCC-Fälle (drei HIV-positive und drei HIV-negative) diag-nostiziert. Davon präsentierten sich zwei NCC-Fälle (ein HIV-positiver und ein HIV-negativer) mit chronisch progressiven Kopfschmerzen und vier Fälle blieben neurologisch unauffällig. In der Gruppe der HIV-infizierten Patienten war ein serologisch positives Ergebnis bei *T. solium* nicht

mit der Höhe der CD4+-Zellzahlen, der Dauer der antiretroviralen Therapie und/oder der Klassifizierung der HIV Erkrankung assoziiert.

Abbildung 11. Rekrutierungszentrum der HIV-positiven Patienten (Haydom Lutheran Hospital in Mbulu District, Nord-Tansania) (Bild: Veronika Schmidt)

Abbildung 12. Rekrutierungsort der HIV-negativen Studienteilnehmer: Dörfer in den umliegenden Distrikten (Bild: Veronika Schmidt)

Schlussfolgerung:

In dieser Studie wurde eine niedrigere *T. solium* Zystizerkose und Täniose Ag- und Ak-Seroprävalenz ermittelt, als bisher veröffentlichte Zahlen für diese Region berichten. Die geringe Anzahl seropositiver Studienteilnehmer kann somit ein möglicher Grund dafür sein, dass in dieser Studie kein Zusammenhang zwischen einem positiven HIV-Status und einer Infektion mit *T. solium* oder NCC-Erkrankung gefunden werden konnte. Es wurde deutlich, dass in diesem Gebiet der Einschluss einer größeren Studienpopulation erforderlich sein wird, um bisherige Schlüsse hinsichtlich der Beeinflussung einer Infektion mit *T. solium* beim Menschen durch eine HIV-Co-Infektion zu bestätigen bzw. zu widerlegen.

Eigenanteil:

Bei dieser Studie übernahm die Doktorandin das gesamte Studienmanagement am Studienort und war in die konzeptionelle Studienplanung mit eingebunden. Sie war verantwortlich für die Organisation und Supervision aller lokalen Studienabläufe im Haydom Lutheran Krankenhaus, Mbulu Distrikt, Nord-Tansania, sowie für die Rekrutierung der Kontrollen in den Studiendistrikten und die Organisation der Patiententransporte. Während mehrmonatiger Aufenthalte vor Ort führte die Doktorandin Trainings der lokalen Feld- und Laborteams sowie des medizinischen Studienpersonals durch und war für das Qualitätsmanagement aller Studienteile verantwortlich. Sie übernahm den Entwurf der Unterlagen zur Datenerhebung, den Dateneintrag sowie – mit Unterstützung der Epidemiologen Prof. Hélène Carabin und Prof. Karl-Heinz Herbinger – die Auswertung der Daten. Nach dem von ihr organisierten Versandt der Serumproben zu den CDC Atlanta, USA, führte die Doktorandin dort die gesamte serologische Testung mittels ELISA- und Immunoblot-Tests durch. Abschließend wurde die entsprechende Veröffentlichung von ihr als Erstautorin verfasst.

4 Allgemeine Schlussfolgerung

Im Rahmen der beiden hier zusammengefassten Studien konnten in den zwei untersuchten speziellen Kohorten – Epilepsiepatienten im per-/urbanen Bereich sowie HIV-co-infizierte Patienten – die Präsenz von TSCT in Tansania nachgewiesen und neue demografische, klinische, serologische sowie radiologische Daten der betroffenen Patienten erhoben werden. Es zeigte sich, dass die Datensammlung in diesen speziellen Kohorten eine große Anzahl von Studienteilnehmern sowie enorme finanzielle Ressourcen und Zeit erfordert, um statistisch signifikante Aussagen treffen zu können. Dies wurde besonders bei dem direkten Vergleich von HIV-co-infizierten Patienten und deren Kontrollgruppe sowie bei der Auswertung der potenziellen Risikofaktoren für TSCT deutlich. Hier konnten aufgrund der zu geringen Anzahl von detektierten TSCT-Fällen nicht alle speziellen Fragestellungen abschließend beantwortet werden. Für die weitere Bearbeitung werden noch größere Kohorten sowie Multicenter-Studien erforderlich sein. Die dieser Dissertationsarbeit zugrundeliegenden Studien stellen jedenfalls die ersten systematischen Untersuchungen mit ausführlichen Falldokumentationen in diesen Kohorten in Subsahara-Afrika dar. Darüber hinaus trugen diese Arbeiten zu einem nachhaltigen interkulturellen Austausch und Wissenstransfer zwischen den deutschen und afrikanischen Projektteams bei.

5 Zusammenfassung

Die TSCT ist ein parasitärer Erkrankungskomplex, der vom Schweinefinnenbandwurm *T. solium* verursacht wird. Diese Zoonose umfasst den Hauptwirt Mensch und den Zwischenwirt Schwein und wird vorwiegend als Gesundheitsproblem der ländlichen Regionen strukturarmer Länder angesehen. Die Hochendemiegebiete befinden sich vor allem in Ländern mit extensiver Schweinehaltung, wie dies in Tansania der Fall ist. *T. solium* gewinnt jedoch auch in ressourcenstarken Ländern als Erreger in der Reise- und Migrationsmedizin sowie im Kontext von der Entwicklung spezifischer Diagnose- und Behandlungsrichtlinien zunehmend an Bedeutung. Die globale Datenlage zur TSCT ist nach wie vor sehr lückenhaft. Für spezielle Kohorten – wie Epilepsiepatienten im urbanen Bereichen oder Patienten mit Co-Infektionen – wurden noch keine systematischen Untersuchungen durchgeführt. Diese Dissertationsarbeit beschäftigt sich nun mit demografischen, klinischen, serologischen und radiologischen Untersuchungen der TSCT in zwei speziellen Kohorten in Tansania:

Im ersten Teil der Arbeit wird der Frage nachgegangen, ob die TSCT in einer afrikanischen Großstadt wie Dar es Salaam, in welcher der Lebenszyklus von *T. solium* kaum komplettiert werden kann, eine Rolle spielt und ob demografische Unterschiede sowie Unterschiede im Risikoverhalten infizierter Personen zu sehen sind. Hierfür wurde eine Gruppe von 302 Epilepsiepatienten in mehreren Gesundheitszentren von Dar es Salaam rekrutiert und klinisch, serologisch sowie radiologisch auf Infektionen mit *T. solium* untersucht. Patienten mit positiven Befunden wurden dann vor Therapie erneut intensiven Folgeuntersuchungen unterzogen, um so genauere Rückschlüsse auf den Status der Infektion ziehen zu können. Der zweite Teil dieser Dissertation beschäftigt sich mit der Frage, ob und inwiefern der HIV-Status eine Infektion mit *T. solium* begünstigt und ob es unterschiedliche Ausprägungen der TSCT bei HIV-co-infizierten Patienten im direkten Vergleich mit HIV-negativen Kontrollen gibt. Hierfür wurden in Nord-Tansania 170 HIV-positive Patienten in einer Klinik sowie 170 HIV-negative Kontrollen – nach Alter, Geschlecht und Wohnort gematcht – in den umliegenden Distrikten rekrutiert, und anschließend auf eine Infektion mit *T. solium* klinisch, serologisch, und radiologisch untersucht.

Im Rahmen dieser mehrjährigen Studien konnten erste wichtige Daten über TSCT für beide speziellen Kohorten gesammelt werden, die in den beiden dieser Dissertation zugrundeliegenden Veröffentlichungen genau dargelegt werden. Es zeigte sich jedoch auch, dass weitere Multicenter-Studien mit einer deutlich größeren Anzahl von Studienteilnehmern erforderlich sein werden, um die primären Fragestellungen für diese speziellen Kohorten abschließend beantworten zu können. Diese Studien trugen darüber hinaus zu einem intensiven Wissenstransfer bei. Es konnten wichtige Aspekte der TSCT im Bereich Prophylaxe, Diagnose und Therapie in peripheren Gesundheitseinrichtungen vermittelt werden, in denen dieser Zoonose bislang noch keine Beachtung geschenkt wurde.

6 Summary

TSCT is a parasitic disease complex caused by the pork tapeworm. This zoonosis includes as main host humans and intermediate host pigs and is predominantly a health problem of rural regions in resource-poor countries. Endemic areas are located mainly in countries with extensive pig keeping, as is the case in Tanzania. However, *T. solium* is becoming increasingly important in resource-rich countries as a pathogen in travel and migration medicine as well as in the context of the development of specific diagnostic and treatment guidelines. The global data on TSCT are still scarce so far. For specific cohorts – such as epilepsy patients in urban areas or patients with co-infections like HIV – no systematic studies have been carried out. This dissertation is now dealing with the clinical, serological and radiological study of TSCT in two special cohorts in Tanzania:

The first part of the thesis explores the question whether TSCT in a large African city like Dar es Salaam, in which the life cycle of *T. solium* can hardly be completed, plays a role, and whether demographic differences and differences in risk behavior of infected persons can be found. In this study a group of 302 epilepsy patients were recruited from several health centers in Dar es Salaam; all participants were examined clinically, serologically, and radiologically for *T. solium* infections. Patients with positive findings were subject to intensive follow-up examinations before therapy in order to be able to draw more accurate conclusions about their status of the infection. The second part of this thesis deals with the question of whether and to what extent the HIV status determines infection with *T. solium* and whether there are differences in the clinical and radiological characteristics of NCC in HIV co-infected patients in direct comparison with HIV-negative controls. In northern Tanzania, 170 HIV-positive patients in a rural clinic and 170 HIV-negative controls – matched by age, gender, and place of residence – were recruited from the surrounding districts, and subsequently clinically, serologically, and radiologically examined for *T. solium* infections.

In these multi-year studies, the first important data on TSCT could be collected for aforementioned specific cohorts, which are presented in the two papers underlying this thesis. However, it has also been shown that further multi-center studies with a significantly larger number of study participants will be required in order to be able to conclusively answer the relevant questions for these specific cohorts. These studies also contributed to an intense transfer of knowledge by addressing and teaching specific aspects of TSCT in healthcare settings where this zoonosis so far has not been standardized.

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Abbildungsverzeichnis

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Anhang A: Veröffentlichung I (Originalarbeit): „*Taenia solium* cysticercosis and taeniasis in urban settings: Epidemiological evidence from a health center-based study among people with epilepsy in Dar es Salaam, Tanzania“

Veronika Schmidt[1,2], Marie-Claire O'Hara[1,3], Bernard Ngowi[4], Karl-Heinz Herbinger[5], John Noh[6], Patricia Procell Wilkins[6], Vivien Richter[7], Christian Kositz[8], William Matuja[9], Andrea Sylvia Winkler[1,2]

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Die entsprechende Rohdatenbank und die CT-Bilder der NCC-Patienten können unter folgendem Link eingesehen werden:

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RESEARCH ARTICLE

Taenia solium cysticercosis and taeniasis in urban settings: Epidemiological evidence from a health-center based study among people with epilepsy in Dar es Salaam, Tanzania

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Abstract

In Africa, urbanization is happening faster than ever before which results in new implications for transmission of infectious diseases. For the zoonotic parasite *Taenia solium*, a major cause of acquired epilepsy in endemic countries, the prevalence in urban settings is unknown. The present study investigated epidemiological, neurological, and radiological characteristics of *T. solium* cysticercosis and taeniasis (TSCT) in people with epilepsy (PWE) living in Dar es Salaam, Tanzania, one of the fastest growing cities worldwide. A total of 302 PWE were recruited from six health centers in the Kinondoni district of Dar es Salaam. Serological testing for *T. solium* cysticercosis-antigen (Ag) and -antibodies (Abs) and for *T. solium* taeniasis-Abs was performed in all PWE. In addition, clinical and radiological examinations that included cranial computed tomography (CT) were performed. With questionnaires, demographic data from study populations were collected, and factors associated with TSCT were assessed. Follow-up examinations were conducted in PWE with TSCT. *T. solium* cysticercosis-Ag was detected in three (0.99%; 95% CI: 0–2.11%), -Abs in eight (2.65%; 95% CI: 0.84–4.46%), and taeniasis-Abs in five (1.66%; 95% CI: 0.22–3.09%) of 302 PWE. Six PWE (1.99%; 95% CI: 0.41–3.56%) were diagnosed with neurocysticercosis (NCC). This study demonstrates the presence of TSCT in Dar es Salaam, however, NCC was only associated with a few cases of epilepsy. The small fraction of PWE with cysticercosis- and taeniasis-Abs may suggest that active transmission of *T. solium* plays only a minor role in Dar es Salaam. A sufficiently powered risk analysis was hampered by the small

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number of PWE with TSCT; therefore, further studies are required to determine the exact routes of infection and risk behavior of affected individuals.

Author summary

Taenia solium cysticercosis and taeniasis is a zoonotic disease complex which affects thousands of people in sub-Saharan Africa. This parasite has a human-pig life cycle and has been considered a public health problem mainly in rural areas. As African towns and suburbs grow rapidly and disproportionally, adequate infrastructure such as sewage systems and clean water often lack while population density, trade, and travel increase. This may lead to the appearance of parasitic diseases formerly considered 'rural' in urban settings. In this study, we searched for evidence of *T. solium* infections in the Kinondoni district of Dar es Salaam, Tanzania. We focused on people with epilepsy (PWE) since epilepsy is one of the most common and severe disorders associated with *T. solium* neurocysticercosis and tested all of them serologically for *T. solium* cysticercosis and taeniasis. We further investigated neurological and radiological characteristics. Our findings show that in our study area in Dar es Salaam 2.65% of PWE had contracted *T. solium* infection at some stage. Neurocysticercosis, as confirmed by neuroimaging, was found only in 1.99% of PWE. This, in combination with the relatively small number of PWE detected with taeniasis antibodies (1.66%), points towards the fact that active transmission of *T. solium* seems to play only a minor role in this urban setting, suggesting that infections may mainly be contracted in rural areas. Further large-scale studies are required to investigate the infection pathways and risk behavior related to *T. solium* infections within urban areas of sub-Saharan Africa.

Introduction

Taenia solium is a worldwide neglected zoonotic helminth with considerable impact, in endemic countries, on infected humans, animals and the livelihood of their communities. In 2015, the World Health Organization (WHO) Foodborne Disease Burden Epidemiology Reference Group (FERG) published estimates of the global burden of 31 bacteria, viruses, parasites, toxins, and chemicals. *T. solium* was identified as the leading cause of deaths from foodborne diseases caused by parasites. In this report, a median of 370,710 global foodborne illnesses, 28,114 deaths and 2,788,426 Disability Adjusted Life Years (DALYs) related to *T. solium* were reported [1]. Yet, in many endemic regions, data on the epidemiology and characteristics of the disease complex attributed to *T. solium* cysticercosis and taeniasis (TSCT) is lacking, which especially applies to urban areas.

Manifestations of *T. solium* in humans can be twofold: taeniasis, the tapeworm infection in the human intestine caused by ingestion of raw and undercooked cysticerci infected pork, and cysticercosis (CC), an infection with larval cysts in multiple organs of pigs and humans. A human tapeworm carrier sheds millions of eggs per day in the stool. Infested human feces are eaten by free-roaming pigs after open defecation or through access to poorly constructed latrines, thereby completing the parasite's human-pig life cycle. Poor sanitary and handwashing habits represent risk factors for people with taeniasis to infect themselves or other individuals living in close proximity via fecal-oral transmission. After ingestion of eggs larvae will hatch and penetrate the stomach and upper intestine walls, thereby further disseminating in the

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body, and finally develop into cysts in muscles, subcutaneous or neuronal tissue with a clear preference for the central nervous system tissue (brain and spinal cord), a condition known as neurocysticercosis (NCC) [2–5]. NCC represents a preventable cause of epilepsy and has been specifically identified as a main cause of late onset-epilepsy in developing countries [6–8].

For Tanzania, little data on human CC and NCC is available. A hospital-based cross-sectional study conducted in northern Tanzania in 2006, revealed the proportion of definitive and probable NCC (classified by Del Brutto [9]) for PWE to be 2.4% and 11.3%, respectively [8]. For the Hai district, Tanzania, the seroprevalence of *T. solium*-Abs in PWE was 2.8% using the rT24-immunoblot and 1.1% were definitively diagnosed with NCC [10]. In a community-based study conducted in Mbulu district in people without epilepsy (non-PWE), the presence of anticysticercal Abs was reported in 16.3% of 544 individuals using a commercial crude Ag immunoblot [11]. Even less data is available for taeniasis: using microscopy/Kato-Katz or a copro-antigen-enzyme linked immunosorbent assay (copro-Ag-ELISA), the taeniasis prevalence in Tanzania ranged from 0.4% to 1.1% and 0.3% to 5.2%, respectively [12–14]. Presence of adult tapeworm Abs detected by the rES33-immunoblot was found in 4.1% of 820 individuals recruited in Mbeya district and in 0.9% of 213 PWE recruited in the Hai district [10, 15].

To date, research activities on TSCT in sub-Saharan Africa have focused on rural populations, where conditions for maintaining the life cycle of the parasite are favorable [16]. As urban areas in Africa continue to grow disproportionally, conditions for transmission of *T. solium* may also be present in many urban and peri-urban settings. The rapid growth of cities often leads to expansion of informal settlements and slums with poor housing, unclean water, the establishment of urban backyard farming, and an inadequate sewage system. Moreover, due to the increase of urban populations and wealth, the demand for pork in towns rises. This goes hand in hand with an increase in informal pig trade and backyard slaughter. Travel of urban populations to and from rural areas also represents a risk factor for the introduction of infectious diseases in towns [17–19]. Rural societies differ from urban societies in terms of demographic patterns, living habits, and co-morbidities. Therefore, data obtained in rural populations should not be applied to urban populations without the generation of evidence. There is clear need for a better understanding of the presence and impact of the TSCT complex in the urban context, as well as of its detailed transmission pathways and specific demographic patterns. To address this gap, we performed a health-center based study in PWE in Dar es Salaam, Tanzania, one of the fastest growing cities in Africa. NCC can be found more often in PWE than in non-PWE [4, 5], which makes this study population ideal to search for evidence of human TSCT in areas where data are not available yet. Hence, the objectives of this study are: 1. to investigate the presence and prevalence of TSCT in PWE in Dar es Salaam, 2. to describe the detailed clinical, serological and radiological characteristics of affected PWE, and 3. to obtain data on associated risk factors for TSCT in PWE living in urban and peri-urban areas.

Methods

Settings

This study was conducted in Dar es Salaam, the former capital of Tanzania, with a population of 4.36 million people, which accounts for 10% of the total population according to the 2012 National Census [20]. With an officially reported annual growth rate of 4.39% in 2012 and an estimated population of 5 million by 2020, Dar es Salaam belongs to the ten fastest growing cities in the world [21]. At the time of this study, the city was divided into three municipalities: northern Kinondoni, central Ilala, and southern Temeke. Our study was conducted in Kinondoni municipality, an area of 531 km^2 with 1.77 million inhabitants in 2012 [22]. The detailed study area is shown in Fig 1.

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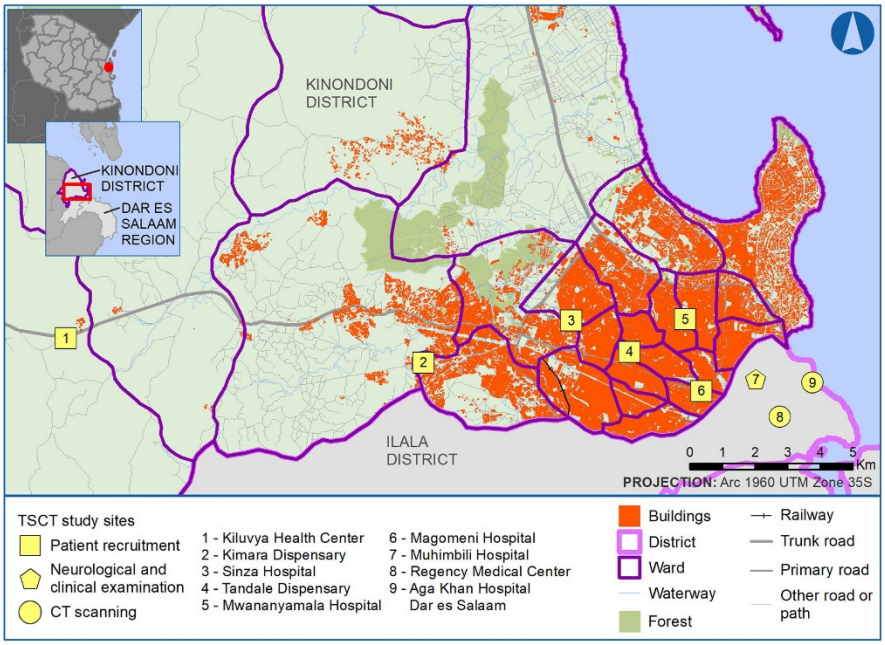

Fig 1. Location of recruitment centers with the distribution of urban and peri-urban areas. Buildings, roads, railways, waterways, and forest data are copyrighted by OpenStreetMap contributors and available from https://www.openstreetmap.org (OpenStreetMap contributors (2016) Planet Dump [Data file from 2016 Aug. 18]). Extract retrieved 2016 Aug. 23 from BBBike, https://download.bbbike.org/osm/). Country, region, district, and ward boundaries are from the GADM database of Global Administrative Areas, v2.8 (November 2015).

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Administratively, Kinondoni encompasses four divisions and 27 different wards. The original inhabitants of this municipality were the Zaramo and Ndengereko, but urbanization led to a multi-ethnic and multi-religious area. Most likely due to the fast growth of the human population, there is an increasing amount of pigs being kept within the city of Dar es Salaam. The overall annual growth rate of the pig population from 1999 to 2008 was 32.5% [22]. For the agricultural year 2007/2008 a total of 35,479 pigs—kept in 1,937 households (5.7% of all households in the city)—with an average of 18 pigs per pig keeping household—was reported for the city and its suburbs [22]. With its fast urbanization, increasing problems due to insufficient infrastructure (e.g. lack of clean water supply and sewage systems), and a multi-ethnic population, Dar es Salaam has become the epitome of a modern East African city, and therefore was selected as the study site for this survey [17, 23].

Definitions

PWE were defined as individuals having more than one afebrile seizure unrelated to acute metabolic disorders or withdrawal of drugs and alcohol [24]. Seropositive CC cases were defined as those individuals positive on the lentil lectin purified glycoprotein enzyme-linked immunoelectrotransfer blot (LLGP-EITB), rT24H-immunoblot, or Ag-ELISA test. Seropositive taeniasis cases were defined as individuals positive on the rES33-immunoblot. Individuals with TSCT were defined as those with a positive result in at least one of the four assays.

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T. solium cysticercosis and taeniasis in Dar es Salaam, Tanzania

Individuals without TSCT were defined as those with negative results on all serological tests performed. NCC cases were defined as seropositive CC individuals with absolute or highly suggestive NCC lesions detected on computed tomography (CT). Classification in absolute and highly suggestive NCC was performed following the revised criteria by Del Brutto et al. [25]. Viable cysts (active NCC) were defined as cystic lesions (with or without visible scolex) or lesions with ring enhancement. Calcified cysts (inactive NCC) were defined as small hyperdense lesions (calcifications on CT scan) with no sign of ring enhancement [26].

Enrollment of study participants

Between March 2012 and December 2013 a health center-based recruitment of PWE was performed by a medical officer of Muhimbili University of Health and Allied Sciences (MUHAS) in six governmental health centers and dispensaries located in six wards of the former Kinondoni municipality—Magomeni Hospital (Magomeni), Tandale Dispensary (Tandale), Kiluvya Hospital (Kibamba), Mwananyamala Hospital (Mwananyamala), Sinza Hospital (Sinza) and Kimara Dispensary (Kimara) (Fig 1).

For two months, health records were screened retrospectively. A total of 698 individuals with epileptic seizures were identified. Besides a general diagnosis of epilepsy, the following inclusion/exclusion criteria were applied: 1. onset of epilepsy above five years of age to exclude febrile seizures, 2. no relevant history of traumatic brain injuries and 3. no past or present history of any substance abuse. Women who reported pregnant were excluded due to ethical reasons as they would not be able to undergo a CT scan. A total of 600 individuals were confirmed as PWE. Due to financial restrictions, not all identified PWE could be included in this study. Subsequently, 302 PWE were randomly selected and invited by phone to participate and to attend the Hospital of MUHAS. A detailed workflow of enrollment and all examinations can be found in Fig 2.

Interview and neurological examination

All eligible individuals were invited to the Neurologic Clinic at MUHAS in order to undergo further examinations for two days. During the first examination day a medical doctor in training from the Technical University of Munich, Germany (MCO), together with a health officer re-confirmed inclusion and exclusion criteria by a face-to-face interview. The process was supervised by a Professor of Neurology of MUHAS (WM). Subsequently, each PWE was asked to answer an in-depth questionnaire (see S1 Document). The questionnaire was adapted from a previously validated questionnaire used in community-based epilepsy studies in different African countries and, in addition, addressed socio-demographic features, pork consumption habits as well as hygienic and sanitary practices [27]. In this questionnaire, epileptic seizures were classified as suggested by Winkler et al. [28]. Participants' mental state, as well as past psychiatric illnesses, were assessed by an experienced neurologist (WM) during the detailed neurological examination. For the diagnosis and classification of psychiatric illnesses, the WHO ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research was applied [29]. The consent form and questionnaire were written in English, translated to Swahili and back-translated to English by two independent translators. The interview was followed by a standard neurological examination performed by the Professor of Neurology (WM) at the Neurology Unit of the Department of Internal Medicine at MUHAS. If subcutaneous nodules were reported, a clinical check was performed on those subjects.

Serological testing

For serological testing, a nurse collected 10 ml of whole blood from the cubital vein of each PWE. Blood samples were then immediately stored at +4˚C. After one to four hours, a medical

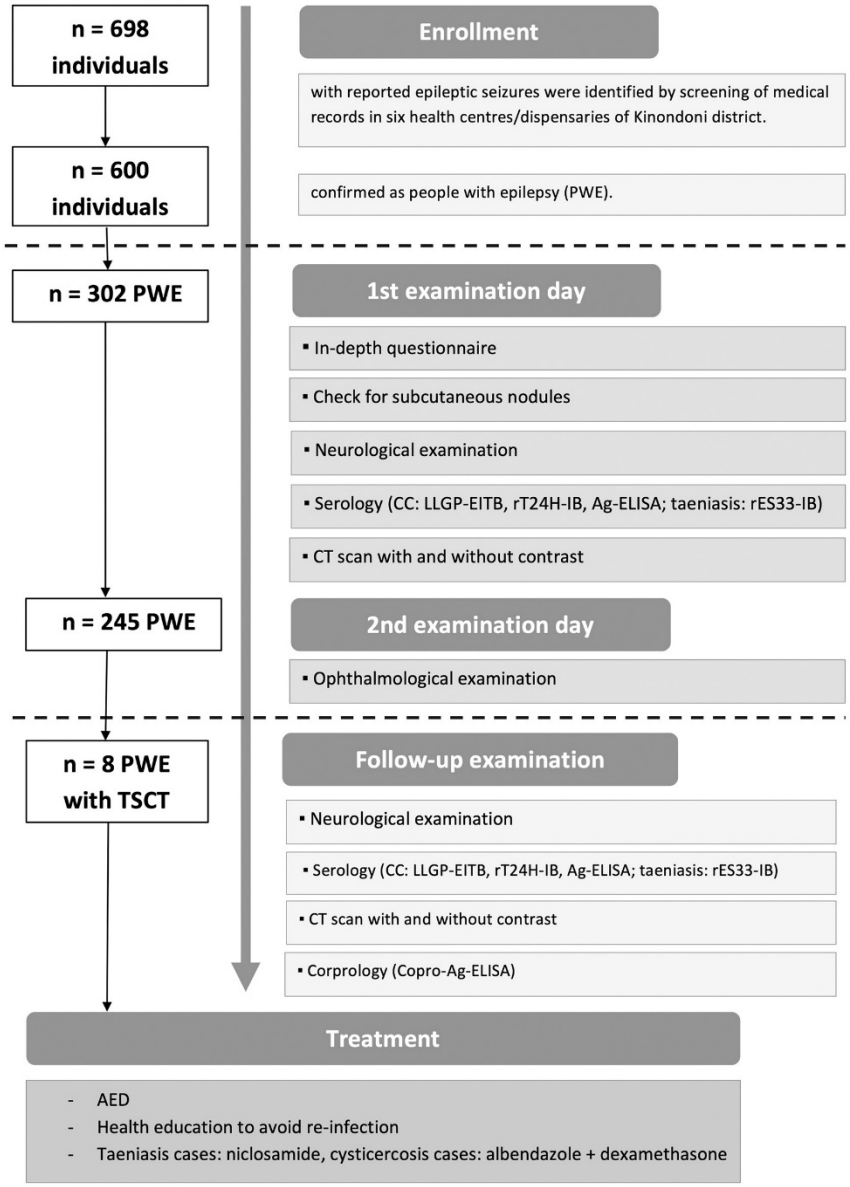

Fig 2. Workflow of recruitment and examinations of people with epilepsy (PWE). CC: cysticercosis; LLGP-EITB: lentil lectin purified glycoprotein enzyme-linked immunoelectrotransfer blot; rT24H-IB: rT24H-immunoblot; Ag: antigen; ELISA: enzyme-linked immunosorbent assay; rES33-IB: rES33-immunoblot; CT: computed tomography; TSCT: *T. solium* cysticercosis and taeniasis; AED: anti-epileptic drugs.

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technician obtained serum by centrifugation at 3,000 rpm for 5 min. On average, two 2 ml vials of serum were obtained from each PWE, and subsequently transported in cool boxes to the Department of Parasitology and Medical Entomology at MUHAS for further storage at–20˚C. Eight to ten months later, samples were transported to the Centers for Disease Control and Prevention (CDC) in Atlanta, USA, for analyses. Two tests were performed to detect CC-specific Abs (LLGP-EITB and rT24H-immunoblot) and one test each to detect CC-specific Ag (Ag-ELISA), and taeniasis-specific Abs (rES33-immunoblot). LLGP-EITB is an enzyme-linked immunoelectrotransfer blot that detects CC-specific Abs to any of the seven glycoproteins [30–32]. The sensitivity and specificity for the LLGP-EITB is 96%, and 97% with more than two brain cysts. In particular, one of the seven diagnostic bands—the glycoprotein (Gp) 50 band—was reported to potentially cross-react with other parasitic infections such as *T. saginata*, *Echinococcus granulosus*, and *Schistosoma ssp*. [32–34]. The rT24H-test is an immunoblot that detects CC-specific Abs to a *T. solium* recombinant Ag with a reported sensitivity of 99% and specificity of 100% [32, 35]. Cross-reactions are described with *Entamoeba histolytica*, *Hymenolepis nana* and *Schistosoma ssp*. [35]. The Ag-ELISA that detects *Taenia solium*.-Ag in serum is a monoclonal Abs (B158/B60 Abs) capture-based ELISA and was performed following a modified protocol as described in Dorny et al. [36]. This test has a sensitivity of 90% and a specificity of 98% for the detection of active *T. solium* infection. To the current state, it cannot be completely ruled out that, this test may cross-react with other *Taenia ssp*., such as *T. saginata*. The rES33-test is an immunoblot that detects adult *T. solium* specific-Abs using a recombinant protein derived from the excretory-secretory proteins of the adult tapeworms with a sensitivity of 99% and a specificity of 99.7% [37, 38]. Cross-reactions with *E. granulosus* and *S. mansonii* were reported in some formats using this Ag [39]. Abs to recombinant peptides, rT24H and rES33 were assessed in the same test [32]. All test results were blinded and then interpreted independently by two scientists (VS and JN) with extensive experience in reading these *T. solium* in-house tests. For quality assurance, each positive test was repeated and 15 randomly selected negative samples were also re-analyzed.

Neuroimaging

After blood collection at MUHAS, PWE were transported by car to external sites for CT scans. Two privately run health facilities with CT scanners in Dar es Salaam were selected for this study due to easy accessibility and high-quality equipment: imaging for 242 PWE was performed at the Regency Medical Center using a 64 slice Philips CT scanner (Philips, Best, The Netherlands). The standard imaging protocol included a non-enhanced and a contrast-enhanced axial scan of the neurocranium with 64 slices and 1 mm slice thickness, with 5 mm slice reconstruction for the cerebrum and 3 mm for the cerebellum. Due to technical problems with this CT scanner, 56 PWE had to be transferred to the Aga Khan Hospital, Dar es Salaam, where the same imaging protocol was performed on a GE CT scanner. CT scan images performed at Aga Khan Hospital were evaluated by radiologists on site and images performed at Regency Medical Center were transferred by telemedicine to radiologists in India for evaluation. Thereafter, all images were stored as hard copies and transferred to the Technical University Munich, Germany, where they were evaluated by a radiologist (VR) and a neurologist experienced in NCC diagnoses (ASW), both of whom were blinded to the clinical diagnosis and the original reporting. One PWE had a CT scan performed within eight months and three patients within one month prior to this study (two at Regency Medical Center and two at Aga Khan Hospital). Records of these former scans were used for evaluation to avoid unnecessary exposure to radiation. CT scans were evaluated for the presence of NCC (viable cysts or calcifications, number of lesions) or any other anomaly.

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Ophthalmological examination

On their second examination day, 245 of 302 PWE (who agreed to participate and presented at the clinic) received an ophthalmological examination by a senior ophthalmologist at the Department of Ophthalmology, MUHAS, including checks for ocular symptoms, measurements of intraocular pressure and visual acuity, fundoscopy and checks for visible cysts under the eyelids, the anterior chamber and other parts of the eye.

Follow-up of PWE with TSCT

All PWE tested positive to at least one of the serological TSCT tests were asked to return to MUHAS for follow-up examinations and treatment. A second neurological examination was performed by the Professor of Neurology at the Department of Internal Medicine (WM) eight to ten months after the first examination. Due to the delay, which was caused by logistic difficulties, all seropositive PWE were re-invited to a second CT scan shortly before treatment at the Department of Radiology, Aga Khan Hospital. In addition, a second blood sample (10 ml from each individual) was taken at the Department of Internal Medicine, MUHAS. Taeniasis-Abs positive patients were treated with niclosamide 2 g as a starting dosage followed by 1g daily for six days. Active NCC cases were given albendazole 15 mg/kg/day for seven days combined with dexamethasone 24 mg/day. All PWE found positive for TSCT received intensive public health education regarding potential auto-infection and deworming to reduce the risk of a new infection. PWE received symptomatic therapy until serological *T. solium* test results were available and decisions on further therapeutic steps could be made. Serum samples were again sent to CDC Atlanta for testing using the same tests as described above. In addition, all seropositive PWE were asked to provide three stool samples (at least 50 ml each) for copro-Ag-ELISA testing before treatment, which was also performed at the CDC Atlanta following a protocol described previously by Guezala et al. This test is described to be species-specific and not to cross-react with *T. saginata* [40].

Data analysis

All data were entered in Excel 2010 (Microsoft, Redmond, WA). All the statistical tests were carried out by EPI INFO 3.3.2. (CDC, Atlanta, GA, USA), and with R statistical software (R version 3.5.2). The descriptive analysis was based on proportions for qualitative variables (Chi-squared test, including Fisher´s exact test) and differences in means for quantitative variables (Mann-Whitney U test). Post hoc tests were performed after categorizing the quantitative variable for the cases in which the Mann-Whitney U test yielded a significant p-value. The outcome of these analyses is presented by p-values, with the statistical significance defined as p-values below 0.05. We considered the Benjamini-Hochberg procedure to evaluate the significance of the individual p-values in the context of the multiple testing [41]. Further, univariate and multivariate logistic regression analysis was performed. Ten socio-demographic (sex, age, school education, religion, occupation, period of residency in Dar es Salaam, pork consumption, pork consumption by family, latrine usage, and intake of anthelmintic drugs in the past 12 months) and seven clinical (chronic progressive headaches, age at first seizure, frequency of seizures per month before treatment, type of seizures, motor activity during seizures, aura present before seizures, and psychiatric illness) variables of relevance were included in the univariate analysis. Only those variables showing a p-value less or equal to 0.10 were included in the subsequent multivariate logistic modelling. The results of the regression analysis are presented as Odds ratios (OR), including 95% confidence intervals (95% CI), and corresponding p-values.

Ethical statement

Ethical approvals for this study were obtained from the Directorate of Research and Publications, MUHAS, Dar es Salaam (Ref. No.: MU/DRP/REC/Vol.I/36, MU/RP/AEC/Vol.Xii/86 and MU/DRP/AEC/Vol.XVI/91) as well as from the Ethical Committee of Ludwig-Maximilian University (LMU) Munich, Germany. The project proposal and export permits for biological material to the USA were also cleared by the National Institute for Medical Research (NIMR), Tanzania, and a material transfer agreement with the CDC Atlanta was obtained.

Risks and benefits of the diagnostic tests including CT scan were explained to potential participants. Women who were pregnant or reported a missed period were excluded from this study. Following Tanzanian regulations, written informed consent was obtained from participants aged 18 years or more, and oral assent from the patient as well as written consent from a parent/guardian was collected, if patients were under the age of 18 years. In the event of illiteracy, forms were read to the participant and fingerprints were taken. All patients received feedback on the results of their CT scan. In case of any pathological finding that required treatment, patients were referred to the appropriate hospital for treatment.

Results

Socio-demographic data and public health characteristics

Three hundred and two PWE were recruited from six health centers and dispensaries of the former Kinondoni district to participate in this study: 108 (35.8%) PWE from Magomeni Hospital, 26 (8.6%) from Tandale Dispensary, 10 (3.3%) from Kiluvya Health Center, 88 (29.1%) from Mwananyamala Hospital, 23 (7.6%) from Sinza Hospital, and 47 (15.6%) from Kimara Dispensary. Locations of recruitment centers are shown in Fig 1.

The total study population comprised of 160 (53.0%) female PWE. The overall age distribution ranged from 6 to 85 years with a median age of 23 years. PWE were distributed over the chosen age bands as follows: age groups 6–19 years, 20–39 years, 40–59 years, and 60–85 years was 111 (36.8%), 147 (48.7%), 38 (12.6%), and 6 (2.0%) (Fig 3).

The majority (231; 76.5%) of PWE were single with 150 (49.7%) being of Christian faith, followed by 149 (49.3%) who were Muslim. Primary school was attended up to seven years by 248 (83.7%) PWE. Only 24 (8.2%) PWE continued schooling after primary school or went for higher education. No school education was reported by 24 (8.2%) PWE.

The group of PWE infected with TSCT comprised of eight individuals. The median age of PWE with TSCT was 29.5 years and ranged from 18 to 60 years with equal sex distribution. There were more (5; 63.0%) PWE with TSCT found amongst Christians than amongst Muslims (3; 38.0%). In the group of PWE without TSCT, 156 (53.1%) were female. The median age was 23 years and the age distribution ranged from 6–85 years (Table 1). Further socio-demographic characteristics as well as associated factors for TSCT are presented in Table 1. None of these variables were found to be significantly different between PWE with and without TSCT.

Neurological and psychiatric characteristics

Anti-epileptic drugs (AED) were taken by all study participants for whom this information was available (268). The most common AED used was Carbamazepine (126; 41.7%) followed by Phenobarbitone (103; 34.1%). The majority of PWE with TSCT (5/8; 62.5%) and PWE without TSCT (162/232; 69.8%) reported suffering from chronic progressive headaches. A family history of epileptic seizures was reported less frequently in PWE with TSCT compared to those without TSCT (1/7 (14.3%) versus 100/289 (64.6%)), although not significant. Reported age at first seizure was significantly higher in PWE with TSCT ($p = 0.03$): it ranged

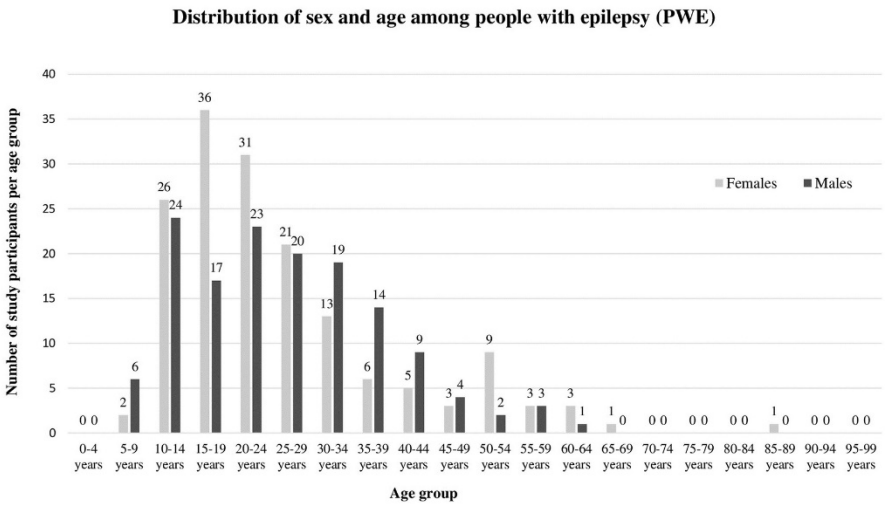

Fig 3. Sex and age distribution of the study population.

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from 14 to 37 years with a median of 22.5 years, whereas in the group of PWE without TSCT age ranged from 9 to 20 years with a median of 14 years. The 31–85 age group showed a significant correlation with TSCT ($p = 0.04$). The mean frequency of 11 seizures per month before treatment was similarly high in both groups. Type of seizure was significantly correlated with TSCT ($p = 0.04$). Tonic/clonic seizures were the most common presentation and seen at a similar percentage in both groups. Aura before seizures was significantly ($p = 0.03$) more often reported by PWE with TSCT (7/8; 87.5%) than by PWE without TSCT (131/294; 44.6%). Injuries that occurred during seizures were common in both groups. Concomitant psychiatric illness was reported in more than half of the patients in both groups. In PWE with and those without TSCT, psychiatric illness was present in 4 of 7 (57.1%) and 159 of 293 (54.1%), respectively. Among the 163 PWE reporting psychiatric illnesses, 83 (50.9%) suffered from psychotic episodes or behavioral problems, 32 (19.6%) showed mental retardation, 50 (30.7%) reported a cognitive decline, and 14 (8.6%) depression. Two of the four affected PWE with TSCT presented with moderate dementia, one individual reported a cognitive decline for two months only and one severe depression. Detailed neurological and psychiatric characteristics of the study population are shown in Table 2.

Logistic regression models

Univariate logistic regression models were calculated for ten socio-demographic and seven clinical independent variables of relevance, and with TSCT as the dependent variable. These individual models indicate that the age at first seizure ($p = 0.06$) and the presence of an aura before seizures ($p = 0.04$) were significantly associated with TSCT. All other variables presented p-values well over the significance limit of 0.10. The results of all individual models are collected in S1 Table.

Variables showing a p-value less than 0.10 were utilized to calculate our final model via a multivariate logistic regression. The results of this multivariate analysis confirm an association of PWE being positive for TSCT and the age at which the first seizure occurs ($p < 0.049$; OR

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Table 1. Socio-demographics and associated factors for *T. solium* cysticercosis and taeniasis among people with epilepsy.

Variables	People with epilepsy						*p*-value[c]
	seropositive for			seronegative for			
	T. solium cysticercosis/and taeniasis						
	Number	Proportions (%)[a]	Proportions (%)[b]	Number	Proportions (%)[a]	Proportions (%)[b]	
Total	8	100	-	294	100	-	
Sex							1.00
Female	4	50.00	-	156	53.06	-	
Male	4	50.00	-	138	46.94	-	
Age							0.24
6–19 years	3	37.50	-	108	36.73	-	
20–39 years	3	37.50	-	144	48.98	-	
40–59 years	1	12.50	-	37	12.59	-	
60–85 years	1	12.50	-	5	1.70	-	
School education							0.71
Data known	7	87.50	100	289	98.30	100	
None	0	0	0	24	8.16	8.30	
≤7 years	6	75.00	85.71	242	82.31	83.74	
8–11 years	1	12.50	14.29	23	7.82	7.96	
Religion							0.74
Christian	5	62.50	-	145	49.32	-	
Muslim	3	37.50	-	146	49.66	-	
Other	0	0	-	3	1.02	-	
Occupation							0.83
Data known	8	100	-	284	96.60	100	
Student	0	0	-	93	31.63	32.75	
Business man/woman	3	37.50	-	37	12.59	13.03	
Medical profession	1	12.50	-	6	2.04	2.11	
Gastronomy	0	0	-	3	1.02	1.06	
Other	0	0	-	27	9.18	9.51	
None	4	50.00	-	118	40.13	41.55	
Period of residency in Dar es Salaam							0.92
Data known	8	100	-	285	96.94	100	
3–10 years	1	12.50	-	48	16.33	16.84	
11–20 years	4	50.00	-	113	38.44	39.65	
21–30 years	0	0	-	73	24.83	25.61	
31–85 years	3	37.50	-	51	17.35	17.89	
Pork consumption							0.72
Data known	8	100	-	292	99.32	100	
Yes	5	62.50	-	150	51.02	51.37	
No	3	37.50	-	142	48.30	48.63	
Pork consumption by family							0.26
Data known	7	87.50	100	292	99.32	100	
Yes	6	75.00	85.71	179	60.88	61.30	
No	1	12.50	14.29	113	38.44	38.70	
Latrine usage							0.55
Data known	8	100	-	236	80.27	100	
Always	7	87.50	-	214	72.79	90.68	

(*Continued*)

Table 1. (Continued)

Variables	People with epilepsy						*p*-value[c]
	seropositive for			seronegative for			
	T. solium cysticercosis/and taeniasis						
	Number	Proportions (%)[a]	Proportions (%)[b]	Number	Proportions (%)[a]	Proportions (%)[b]	
Sometimes	1	12.50	-	22	7.48	9.32	
Intake of anthelmintic drug in the past twelve months							0.45
Data known	8	100	-	224	76.19	100	
Yes	1	12.50	-	64	21.77	28.57	
No	7	87.50	-	160	54.42	71.43	

[a] Proportions among the total number of people with epilepsy, regardless of their data being known or not.

[b] Proportions among the total number of people with epilepsy, whose data are known.

[c] Fisher's exact test was used if at least one cell of the contingency table was below 5.

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1.05; 95% CI: 1.02–1.08), as well as with having an aura before seizures ($p = 0.025$; OR 14.85; 95% CI: 4.47–49.35).

T. solium taeniasis antibodies among PWE

Five PWE positive for taeniasis-Abs out of a total of 302 (1.7%; 95% CI: 0.2–3.1%) were identified during the first and second serological testing. One positive PWE lived in Magomeni, three in Mwananyamala, and one in Kimara ward. At the time of the first serological testing, two out of 302 (0.7%; 95% CI: 0–1.6%) PWE were found positive for taeniasis-Abs. Both PWE were male and 32 and 39 years old. One patient was a businessman and the other was a lab technician. One reported to always use latrines and the other only sometimes. Recruitment centers where PWE with taeniasis-Abs were identified during the first examination are shown in S2 Table.

At the follow-up testing—around eight to ten months later—, both PWE with previously confirmed circulating taeniasis-Abs showed negative results. At this time, three additional (1.0%; 95% CI: 0–2.1%) PWE with TSCT showed positive taeniasis-Abs titers: one was a business man who was 44 years old. He reported to use latrines regularly, and he had taken anthelmintic drugs in the past, but could not specify when and which drug exactly. The two others were Muslim women at the age of 18 years, and both reported to never eat pork, but one reported that the family ate pork. All other (3/5) taeniasis-Abs positive cases identified in this study were Christians reporting to eat pork. The copro-Ag-ELISA, performed at the follow-up examination, was negative in all five PWE identified with circulating taeniasis-Abs (Table 3).

T. solium cysticercosis antibodies and antigen

At the time of the first serological testing, eight out of 302 PWE were found positive for CC-Abs (2.7%; 95% CI: 0.8–4.5%), and three of them also showed positive CC-Ag results (1.0%; 95% CI: 0–2.1%; Table 3). Recruitment centers where PWE with CC-Abs and CC-Ag were identified at the first examination are shown in the S2 Table.

At the time of follow-up—eight to ten months later and shortly before treatment—, a second blood sample was taken from those PWE with TSCT. Only four out of eight PWE with initial Abs positive titers showed still a strong positive result in the full LLGP-EITB. One PWE showed a weak positive full LLGP-EITB, two PWE showed only a positive Gp50 band and one sero-reverted.

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T. solium cysticercosis and taeniasis in Dar es Salaam, Tanzania

Table 2. Neurological and psychiatric characteristics of people with epilepsy seropositive and seronegative for *T. solium* cysticercosis and taeniasis.

Variables	People with epilepsy						*p*-value[c]	Post hoc *p*-value
	seropositive for *T. solium* cysticercosis/and taeniasis			seronegative for *T. solium* cysticercosis/and taeniasis				
	Number	Proportions (%)[a]	Proportions (%)[b]	Number	Proportions (%)[a]	Proportions (%)[b]		
Total	8	100	-	294	100	-		
Type of anti-epileptic drug (AED)							1.00	
Data known	8	100	-	260	88.44	100		
Carbamazepine	4	50.00	-	122	41.50	46.92		
Phenobarbitone	3	37.50	-	100	34.01	38.46		
Combination / other AED	1	12.50	-	38	12.93	14.62		
Chronic progressive headaches							0.70	
Data known	8	100	-	232	78.91	100		
Yes	5	62.50	-	162	55.10	69.83		
No	3	37.50	-	70	23.81	30.17		
Family history of seizures							0.43	
Data known	7	100	-	289	98.30	100		
Yes	1	14.29	-	100	34.01	34.60		
No	6	85.71	-	189	64.29	65.40		
Age at first seizure							0.03*	
Data known	8	100	-	291	98.98	100		
5–10 years	0	0	-	100	34.01	34.36		0.06
11–20 years	4	50.00	-	128	43.54	43.99		0.74
21–30 years	1	12.50	-	35	11.90	12.03		1.00
31–85 years	3	37.50	-	28	9.52	9.62		0.04*
Frequency of seizures per month before treatment							0.61	
Data known	8	100	-	284	96.60	100		
0.08–0.9	2	25.00	-	49	16.67	17.25		
1.0–1.9	2	25.00	-	60	20.41	21.13		
2.0–2.9	1	12.50	-	60	20.41	21.13		
3.0–9.9	0	0	-	55	18.71	19.37		
>10	3	37.50	-	60	20.41	21.13		
Type of seizures							0.04*	
Gwa	2	25.00	-	171	58.16	-		0.08
Goa	1	12.50	-	44	14.97	-		1.00
Gua	0	0	-	2	0.68	-		1.00
Gfs	3	37.50	-	66	22.45	-		0.39
Gbd	0	0	-	11	3.74	-		1.00
Sp	2	25.00	-	0	0	-		<0.01*
Motor activity during seizures							1.00	
Tonic	0	0	-	28	9.52	-		
Clonic	0	0	-	12	4.08	-		
Tonic / clonic	7	87.50	-	208	70.75	-		
None	1	12.50	-	46	15.65	-		
Aura present before seizures							0.03*	
Yes	7	87.50	-	131	44.56	-		
No	1	12.50	-	163	55.44	-		
Injuries during seizures							0.55	

(*Continued*)

Table 2. (Continued)

Variables	People with epilepsy						*p*-value[c]	Post hoc *p*-value
	seropositive for			seronegative for				
	T. solium cysticercosis/and taeniasis							
	Number	Proportions (%)[a]	Proportions (%)[b]	Number	Proportions (%)[a]	Proportions (%)[b]		
Data known	8	100	-	293	99.66	100		
Bruise/hematoma	2	25.00	-	37	12.59	12.63		
Burn injury	0	0	-	11	3.74	3.75		
Other	0	0	-	5	1.70	1.71		
None	6	75.00	-	240	81.63	81.91		
Psychiatric illness							1.00	
Data known	7	87.5	100	293	99.66	100		
Yes	4	50.0	57.14	159	54.08	54.27		
No	3	37.5	42.86	134	45.58	45.73		

Gwa: generalized seizures that started within a specific age range (seizures most likely due to idiopathic epilepsy); Goa: generalized seizures that started outside the age range of idiopathic epilepsy but without any obvious sign or history of an underlying cause; Gua: generalized seizures with unknown age of onset; Gfs: generalized seizures with obvious focal neurological signs; Gbd: generalized seizures with more widespread brain damage; Sp: simple partial seizures.

[a] Proportions among the total number of people with epilepsy, regardless of their data are known or not.

[b] Proportions among the total number of people with epilepsy, whose data are known.

[c] Fisher's exact test was used if at least one cell of the contingency table was below 5.

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In three out of eight PWE with TSCT, a positive CC-Ag titer was detected in the first examination and remained positive in the second examination. All three CC-Ag positive PWE showed viable cysts in the CT scan. One CC-Ag positive PWE did not show any lesions in the first CT scans but did on the follow-up scan.

Three PWE with CC-Ab and/or -Ag (P1, P3, P5) were Muslims and five were Christians. Detailed serological Abs and Ag follow-up results in combination with neuroimaging are shown in Table 3.

T. solium neurocysticercosis

In this study, a total of six out of 302 (2.0%; 95% CI: 0.4–3.6%) PWE were identified with definitive NCC classified according to the revised criteria of Del Brutto [25]. At the first examinations five (1.7%; 95% CI: 0.2–3.1%) PWE with NCC and at the follow-up one additional NCC patient were diagnosed. Two of eight PWE with TSCT showed no lesions compatible with NCC on CT scan.

Four of six PWE with NCC were males, and the age range was 18–60 years. One PWE with NCC was Muslim and five were Christians. Five individuals reported having suffered from epilepsy for five years and less, and one for nine years. The age at seizure onset ranged from 14 to 59 years. All patients with NCC had multiple lesions. CT scans showed only calcifications in three patients, two patients had calcifications and viable cysts and one patient was diagnosed with only viable cysts. Chronic progressive headache was reported by three of the six PWE with NCC (two of them showed active lesions) and psychiatric symptoms were found in two (moderate dementia and severe depression) of the five patients with available data (one of them with active lesions) (Table 3).

Of the two patients with calcifications and viable cysts, one had multiple scattered calcified nodules bilaterally and an 8 mm temporo-occipital cyst left with minimal eccentric

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T. solium cysticercosis and taeniasis in Dar es Salaam, Tanzania

Table 3. Serological, neurological and radiological characteristics of people with epilepsy seropositive for *T. solium* cysticercosis and taeniasis.

Variables	Patient number (P)							
	P1	P2	P3	P4	P5	P6	P7	P8
Age (years)	19	39	18	27	18	60	44	32
Sex	female	male	female	male	female	female	male	male
Definitive NCC case[a]	no	yes	yes	yes	no	yes	yes	yes
Epileptic seizures since (years)	7	4	4	9	7	1	3	5
Age when epileptic seizures started (years)	13	35	14	18	11	59	41	27
Chronic progressive headaches	yes	no	yes	no	yes	yes	yes	no
Psychiatric symptoms	yes	no	NK	no	yes	yes	yes	no
Laboratory findings (1st examination)								
CC-Ag	n	p	n	n	n	n	p	p
CC-Abs (LLGP)	p	p	p	p	Gp50	p	p	p
CC-Abs (rT24H)	p	p	p	p	n	p	p	p
Taeniasis-Abs	n	p	n	n	n	n	n	p
Computed tomography findings (1st examination)								
Calcifications	no	yes	yes	yes	no	yes	yes	no
Viable cysts	no	yes	no	no	no	no	yes	no
Number of lesions	none	mult	mult	mult	none	mult	mult	none
Perifocal edema	no	yes	no	no	no	no	yes	no
Laboratory findings (2nd examination)[b]								
CC-Ag	n	p	n	n	n	n	p	p
CC-Abs (LLGP)	Gp50	(p)	p	p	p	Gp50	p	n
CC-Abs (rT24H)	n	p	p	p	p	(p)	p	n
Taeniasis-Abs	n	n	(p)	n	(p)	n	p	n
Copro-Ag[c]	n	n	n	n	n	n	n	n
Computed tomography findings (2nd examination)[b, d]								
Calcifications	no	yes	yes	yes	no	yes	yes	yes
Viable cysts	no	no	no	no	no	no	yes	yes

CC: cysticercosis; Ag: antigen; Abs: antibodies; NCC: neurocysticercosis; NK: not known; LLGP: lentil lectin purified glycoprotein enzyme-linked immunoelectrotransfer blot; rT24H: rT24H-immunoblot; p: positive; n: negative; (p): weak positive; Gp50: only the glycoprotein 50-band was detected on the strip; mult: multiple.

[a] According to the revised diagnostic criteria proposed by Del Brutto [25] and based on both examinations.

[b] Follow-up after eight to ten months.

[c] Copro-Ag testing by an enzyme-linked immunosorbent assay could only be performed with the samples of the 2nd examination due to study limitations.

[d] No information about number and lesions and perifocal edemas were available from the second CT scans, except P8 who had multiple calcifications and viable cysts.

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calcification and another 9 mm occipital cyst left, without edema; additionally, mildly enhancing nodules with minimal surrounding edema were found in the frontal lobes bilaterally, the largest measuring 6 mm, and an 8 mm ring-enhancing lesion was seen in the left caudate nucleus. This patient reported no chronic progressive headache and no psychiatric symptoms. The second active NCC patient showed focal white matter edema in the left parietal lobe, a 10 mm cyst with a central isodense nodule in the left caudate nucleus and an 8 mm cyst in the right occipital lobe, additionally, microcalcifications were noted in the temporal lobes and basal ganglia bilaterally. This patient reported chronic progressive headache and severe depression. The PWE with TSCT that was identified with NCC during the follow-up had multiple calcifications and viable cysts. Further radiological details were not available. The patient reported chronic progressive headache but no psychiatric symptoms.

All six NCC patients were CC-Abs positive on both immunoblot, and three were positive on the CC-Ag-ELISA. All PWE with a positive result in the CC-Ag-ELISA had active lesions. Four of six PWE with NCC also had a positive taeniasis-Abs titer.

Detailed serological, neurological and radiological characteristics of PWE with positive TSCT serology with and without NCC at the time of the first examination and the time of follow-up (eight to ten months later) are shown in Table 3.

Subcutaneous nodules and ocular cysts

There were no subcutaneous nodules found suspicious for *T. solium* cysts in any of the 297 PWE, that presented for this examination. Also, the ophthalmological examinations, performed in 245 (81.2%) out of 302 PWE revealed no *T. solium* cyst or other *T. solium* related changes in the eye or under the eyelids. Fifty-seven PWE did not agree to participate in the ophthalmological examinations or were not presenting at the clinic.

Discussion

For decades, TSCT has been representing a public health concern in the rural areas of endemic countries. Although Praet et al. demonstrated in 2010 that CC infected pigs reach urban markets of Kinshasa in the Democratic Republic of Congo (DRC) [42], the potential presence of TSCT in urban settings has not yet been explored systematically. Therefore, TSCT prevalence and the impact of this zoonotic disease in urban African settings remains unknown. The current study presents first data on human TSCT in one of the fastest growing cities of Eastern Africa, Dar es Salaam. The core dataset of the study is based on a well-documented demographic, diagnostic, and clinical workup of PWE infected with TSCT. The presence of TSCT in Dar es Salaam was clearly demonstrated in this study. However, prevalence estimates of taeniasis, CC, and NCC in PWE are comparable (taeniasis- and CC-Ab) or lower (CC-Ag and NCC) compared to some estimates reported in rural settings. The proportion of taeniasis-Abs among PWE found in the present study is 1.7%, which is comparable with those recently reported from rural districts in Tanzania, that range from 1.2% (n = 170; non-PWE; by rES33-immunoblot) in southern Tanzania to 4.1% (n = 830; non-PWE; by rES38-immunoblot) in northern Tanzania [17, 43, 44]. Previous estimates of taeniasis prevalence in non-PWE based on copro-Ag-ELISA results mostly vary from 0.1% to 4% in community-based settings [15, 45]. Regarding taeniasis prevalence estimates, it has to be considered that specifically the rES38-immunoblot and most copro-Ag-ELISA protocols used in these studies are known to cross-react with *T. saginata*, which might have contributed to some of the higher reported rates. Although the information is still scarce, a recent review revealed that *T. saginata* is present in Tanzania and that it is generally widespread in humans and cattle in Eastern Africa [46].

All PWE identified in the present study with a positive taeniasis-Abs titer also have a positive CC-Abs result. Despite the number of PWE with taeniasis-Abs being relatively small (five including results of the serological follow-up), this could potentially point to a high potential of auto-infection. Evidence for the risk of auto-infection has already been demonstrated by Garcia and Del Brutto (1999), who reported that patients with massive brain infections have a higher probability of carrying a tapeworm (11 patients, 82% with tapeworm infection) [47], and by Gilman et al. (2000), who showed that the frequency of taeniasis in NCC patients may reach 15% [48]. However, all PWE with taeniasis-Abs tested negative in the copro-Ag-ELISA. Two of those PWE presented negative Ab results eight to ten months later during the second examination when the copro-Ag ELISA was performed. This sero-reversion could be explained by a transient infection that was cleared and did not result in detectible Ag levels in

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the stool. However, during the second examination in three formally negative PWE taeniasis-Abs were detected (two showing only a light positive result) whilst the copro-Ag test which was performed at the same time was negative. Besides a recent new exposure, a false positivity due to cross-reacting parasites could potentially explain this discrepancy. Both, the rES33 immunoblot and the copro-Ag-ELISA protocol described by Guezala et al. (2009) have not been reported to cross-react with *T. saginata* [38–40]. However, in previous studies using different formats (like a multiantigen print immunoassay) the rES33-antigen showed cross-reactions with *E. granulosus* and with *S. mansonii* [39], which are both prevalent in Tanzania [49, 50]. The study of the latter was conducted in Dar es Salaam [50]. A microscopic and molecular examination of stool samples might have provided a clearer picture. Unfortunately, they could not be included due to study limitations.

Overall, our taeniasis-Ab results suggest that new *T. solium* infections caused by ingestion of infested pork is probably scarce in Dar es Salaam and that active transmission of *T. solium* may only play a minor role within the urban environment. The study performed by Praet et al. (2010) in Kinshasa already suggested that highly infected animals are excluded at a certain level in the pig trade chain to urban markets. Although low infected pork may reach urban markets and street kitchens, the infection pressure on exposed humans in urban settings seems to be low [42]. This is also supported by the fact that pigs are mainly kept in confinement in these urban surroundings, with no access to human stool. In the present study, all PWE with TSCT reported a residency in Dar es Salaam of at least six years. However, a detailed travel history was not collected, and therefore, it is not unlikely that *T. solium* infections may have been obtained during a trip to endemic rural areas (e.g. for visiting relatives). From a public health perspective, it has to be considered that tapeworm carriers in towns are potentially able to put more people at risk when compared to rural settings. Relevant urban conditions include an increased number of people using one shared pit latrine, increased number of pit latrines of which many are inadequate especially during flooding in wet seasons, small distances between pit latrines and wells, and disposal of feces in plastic bags in slum areas. These conditions may support increased human-to-human transmission and contamination of the environment [51–53]. Given that most NCC patients in this study seem to have been exposed to at least one adult tapeworm it may be useful to routinely examine the stool of NCC patients for *T. solium* eggs and provide intensive public health education on prevention of TSCT re-infections.

Interestingly, three out of eight PWE with TSCT identified in this study were businessmen/women and one PWE was a lab technician. It could be that some professions are at a higher risk and need specific attention and access to information for prevention. Moreover, two taeniasis-Ab positive PWE were of Muslim faith who reported never to eat pork. However, one Muslim NCC patient (P3) with a positive taeniasis-Ab result reported that her family consumed pork. This points to *T. solium* infections potentially being present in Muslim communities in Tanzania. Therefore, *T. solium* infections should not be excluded *a priori* in these communities. For quality assurance all positive tests were repeated in this study; nevertheless, we would like to emphasize that false positivity caused by parasitic cross-reaction cannot be excluded in these cases.

CC-Abs were present in 2.7% PWE. This result is in agreement with a seroprevalence of 2.8% among PWE from a door-to-door study (n = 218) conducted in the Hai district, Tanzania [10], and a seroprevalence of 1.8%, from a study (n = 278) conducted in Ifakara, Tanzania, among PWE [43]. In both cases, studies were performed in rural areas and calculations were based on rT24-immunoblot results.

A large variety of prevalence estimates can be seen in the percentages of CC-Ag among PWE. In the present study, the proportion of 0.99% is comparable with the proportion

reported from a case-control study (1.4%; n = 210) conducted in PWE in rural settings in The Gambia [54]. Nevertheless, the majority of studies conducted in rural African communities indicate higher prevalence estimates for CC-Ag among PWE, ranging up to 23.2% as reported from Zambia [55–57]. All these studies, including ours, used the same Ag-ELISA (B158/B60-ELISA) for Ag-testing. It cannot be totally ruled out, that the higher values are the result of other *Taenia ssp*. infections, such as *T. saginata*, or different cut-off values used for reading the ELISA. However, in our study Ag-ELISA results fit together well with the neuroimaging results; all CC-Ag positive PWE showed active lesions on CT-scan.

Among our eight PWE identified with positive TSCT serology, six had definitive NCC according to the revised criteria of Del Brutto et al. [25], and the overall proportion of definitive NCC in our study is 1.99%. The review of Bruno et al. (2013) describes median urban NCC prevalence estimates in PWE in Latin America from 1.2% (Brazil) to 5.4% (Peru) based on CT scan and LLGP-EITB results [58], the former close to our results. Also, the proportion of NCC in this report is lower than that from a hospital-based cross-sectional study conducted in northern rural Tanzania in 2006 in 212 PWE, which revealed a proportion of definitive NCC of 2.4% based on Ab-detection and CT scan imaging following the revised diagnostic criteria for NCC by Del Brutto et al. [3, 25]. A cross-sectional, community-based study performed in rural Zambia in 49 PWE, reported a proportion of 4.1% (using CT scan and Ag-ELISA results) [57], and a health center-based study in southern Rwanda reported 7.4% of definitive NCC in 215 PWE based on CT scan and Ab-ELISA results [59]. All three African studies were conducted in rural communities. When comparing prevalence estimates in PWE from previous studies to those in our study, our findings indicate that NCC in Dar es Salaam only affects a very small proportion of PWE. Nonetheless, the presence of NCC cases indicates that both serological and radiological diagnostics, as well as appropriate training of medical staff in *T. solium* infections are important for early-case detection and therapy. However, there are currently no serological *T. solium* tests available in Tanzanian laboratories and PWE are currently not tested for NCC (Dr. Bernard Ngowi, pers. comm.).

Along with epilepsy, chronic progressive headaches and psychiatric conditions are the main clinical symptoms/signs of NCC [5]. In the present study, out of six PWE with NCC one had moderate dementia and one reported severe depression. Three of six NCC patients reported chronic progressive headaches. Two of those PWE showed active lesions on CT scan. Whether the headaches were due to brain infection or epilepsy itself cannot be ascertained. Most PWE with negative TSCT results also reported headaches.

Seizure types among PWE with NCC are described in the literature to be very heterogenic. This was also confirmed by Singh et al. [60], who reported that 34.6% of PWE with NCC had seizures of any type ($p < 0.001$). In our study, which identified and examined only eight PWE with TSCT, focal seizure types prevailed in PWE with TSCT which was further supported by the fact that PWE with TSCT reported significantly more often an aura ($p = 0.03$), which in itself represents a focal seizure, compared to PWE without TSCT. In our study, the type of seizure was significantly correlated with TSCT ($p = 0.04$). However, results regarding the type of seizure should be interpreted with great caution due to the lack of statistical power and due to the fact that the subgroup 'Simple partial seizures´ included only two cases. The univariate logistic analysis that we performed did not show a significant association between the type of seizure and TSCT in PWE ($p = 0.58$). However, in both logistic regression analysis, the univariate ($p = 0.04$) and the multivariate ($p = 0.049$), having an aura before seizures were clearly associated with TSCT. Despite NCC being considered a major cause of late-onset epilepsy in endemic countries, the age group (31–85 years) at seizure onset that was significantly correlated with NCC in the bivariate analysis ($p = 0.04$) and the logistic regression analysis ($p = 0.025$) is still higher than age ranges described in other studies [60–62]. A reason for this could

be that the home environment is less contaminated with *T. solium* eggs, henceforth infection is acquired in later adult life when eating in public places as well as moving and travel becomes more frequent.

Regarding serology, all six NCC patients were CC-Abs positive, but only three were positive in the CC-Ag-ELISA (all three with active lesions on CT scan). Therefore, our results suggest that in addition to neuroimaging both—CC-Ab and -Ag testing—should be performed for diagnosis in NCC suspected individuals. Interestingly, two PWE with negative rT24H results and no lesions on CT scan showed at the same time a single positive band (Gp50) on the LLGP-EITB, but were clearly CC-Ab positive in both tests at the respective other examination. This can point towards a very early stage of infection or towards a false-positive result for *T. solium* [33, 34]. A recent study reported reactions of this specific band with *T. hydatigena* and *E. granulosus* in pigs [63]. Cross-reactions in humans with malignancies like lung cancer or other parasitic diseases (like *T. saginata*, *E. granulosus*, and potentially *Schistosoma ssp.*) were linked with a positive GP50 band only [33–35].

We would like to point out the present study has several limitations: first, the study population comprised only PWE. We considered PWE as an ideal study population in order to search for TSCT in a setting with no previous epidemiological information available, as there is good evidence that higher TSCT prevalence estimates are found in PWE [6, 7, 9, 64, 65]. Hence, it must be considered that the prevalence of TSCT in the general population is probably lower. Second, the catchment area of this study covered only one of three municipalities of Dar es Salaam. To get a more precise prevalence estimate of TSCT in Dar es Salaam, further studies covering different urban areas, including larger sample sizes, would represent an asset. Third, our study was limited by the inability to include copro-Ag testing in the initial recruitment phase and microscopic or molecular testing of stool samples due to financial restrictions. This would have provided a more complete picture of taeniasis and whether potential cross-reacting parasites among affected PWE were present. In addition, electroencephalography and MRI, which could not be included, again due to financial restrictions, would have been of added value and should be included in future studies focusing on PWE. Fourth, there was only a small number of TSCT positive PWE identified in this study which prevented a sufficiently powered risk analysis. Therefore, regarding statistics, our findings have to be interpreted with caution. Last, questions regarding personal hygiene, travel, eating habits were very limited and partially missing. A more detailed questionnaire and epidemiological follow-up of people with TSCT should also be included in future studies in order to get detailed information about past travel histories and infection modes of individuals with TSCT in urban settings.

Regarding AED treatment of enrolled PWE it has to be considered that the data used in this study is not representative of the treatment compliance of PWE in Dar es Salaam. In our study, all PWE took AED as the recruitment was performed in health centers and dispensaries providing these drugs and dealing with PWE on regular treatment. Hunter et al. described in 2016 a large epilepsy treatment gap (ETG) in rural Tanzania of 40.5% [66]. A review of ETG in African countries reported a mean of 46.8% [67]. Therefore, it must be assumed that a treatment gap is also present in the urban PWE population of Dar es Salaam, but further studies would be required.

Conclusions

In conclusion, based on the examination of PWE our study demonstrates the presence of TSCT in Dar es Salaam and prevalence of definitive NCC of 1.99% underlining the need of serological and radiological diagnostic capacities as well as training and awareness-raising of medical staff in urban settings. However, we emphasize that the prevalence of CC-Abs and

taeniasis-Abs identified in this study is low, 2.65% and 1.66% respectively. This suggests that active *T. solium* transmission in Dar es Salaam is likely to play only a very minor role. Infections might mostly be contracted during travel to rural areas, or through contaminated food reaching urban markets and street kitchens in town. Adult worm carriers visiting the town for business or family issues might represent another rare source of *T. solium* egg-inflow. Completion of the *T. solium* life cycle in Dar es Salaam seems to be unlikely, though not totally impossible. Follow-up studies with a larger number of TSCT positive individuals, including a more detailed risk assessment, as well as species-specific coprological tests, are required in order to investigate this topic further.

Supporting information

S1 Checklist. Completed STROBE checklist for the study '*Taenia solium* cysticercosis and taeniasis in urban settings: Epidemiological evidence from a health-center based study among people with epilepsy in Dar es Salaam, Tanzania'.
(PDF)

S1 Document. Patient questionnaire used in this study: Protocol for new patient.
(PDF)

S1 Table. Association of socio-demographic and clinical variables and TSCT in people with epilepsy obtained by univariate logistic regression analysis.
(PDF)

S2 Table. Distribution of *T. solium* cysticercosis and taeniasis among people with epilepsy in the recruitment centers of Kinondoni district (1st examination).
(PDF)

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Anhang B: Veröffentlichung II (Originalarbeit): „Association between *Taenia solium* infection and HIV/AIDS in northern Tanzania: a matched cross-sectional study“

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Infectious Diseases of Poverty

RESEARCH ARTICLE Open Access

Association between *Taenia solium* infection and HIV/AIDS in northern Tanzania: a matched cross sectional-study

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Abstract

Background: The frequency of *Taenia solium*, a zoonotic helminth, is increasing in many countries of sub-Saharan Africa, where the prevalence of the human immunodeficiency virus (HIV) is also high. However, little is known about how these two infections interact. The aim of this study was to compare the proportion of HIV positive (+) and negative (–) individuals who are infected with *Taenia solium* (TSOL) and who present with clinical and neurological manifestations of cysticercosis (CC).

Methods: In northern Tanzania, 170 HIV+ individuals and 170 HIV– controls matched for gender, age and village of origin were recruited. HIV staging and serological tests for TSOL antibodies (Ab) and antigen (Ag) were performed. Neurocysticercosis (NCC) was determined by computed tomography (CT) using standard diagnostic criteria. Neurological manifestations were confirmed by a standard neurological examination. In addition, demographic, clinical and neuroimaging data were collected. Further, $CD4^+$ cell counts as well as information on highly active antiretroviral treatment (HAART) were noted.

Results: No significant differences between HIV+ and HIV– individuals regarding the sero-prevalence of taeniosis-Ab (0.6% vs 1.2%), CC-Ab (2.4% vs 2.4%) and CC-Ag (0.6% vs 0.0%) were detected. A total of six NCC cases (3 HIV+ and 3 HIV–) were detected in the group of matched participants. Two individuals (1 HIV+ and 1 HIV–) presented with headaches as the main symptom for NCC, and four with asymptomatic NCC. Among the HIV+ group, TSOL was not associated with $CD4^+$ cell counts, HAART duration or HIV stage.

Conclusions: This study found lower prevalence of taeniosis, CC and NCC than had been reported in the region to date. This low level of infection may have resulted in an inability to find cross-sectional associations between HIV status and TSOL infection or NCC. Larger sample sizes will be required in future studies conducted in that area to conclude if HIV influences the way NCC manifests itself.

Keywords: *Taenia solium*, Taeniosis, Cysticercosis, Neurocysticercosis, HIV, AIDS, Co-infection, Helminth, Tapeworm, Prevalence

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Multilingual abstracts

Please see Additional file 1 for translations of the abstract into the six official working languages of the United Nations.

Background

Taenia solium is a zoonotic parasite which has considerable impact on human and animal health as well as on the agricultural and health sectors in many low income countries [1]. In humans, the adult stage of the tapeworm is found in the intestines (taeniosis) and the larval stage can develop as cysticerci mainly in the subcutaneous tissue, skeletal and heart muscles (cysticercosis, CC), and of most concern for public health, in the brain (neurocysticercosis, NCC) [2–4].

NCC is believed to be the most common helminthic infection of the central nervous system (CNS) worldwide and is well known as a major cause of acquired epilepsy or epileptic seizures resulting in reduced quality of life, social stigma, and high care costs for affected individuals and their caretakers [5–7]. In areas where the infection is endemic, it is estimated that 30% of people with epilepsy (PWE) show lesions of NCC in their brain [8]. In a hospital-based cross-sectional study conducted in northern Tanzania in 2006, definitive and probable NCC (as classified by Del Brutto et al.) was found in 2.4 and 11.3% of PWE, respectively [9, 10]. In Zambia, in a cross-sectional community-based study among PWE, 4.1% could be revealed as definitive NCC and 24.5% as suggestive NCC. In the same study, 2.5 and 0.0% of controls in the non-PWE group were defined as definite and suggestive NCC [11]. Besides epilepsy, other clinical manifestations such as acute and chronic headaches, signs or symptoms of intracranial hypertension, neuropsychiatric disorders and focal neurological deficits have been described [6, 12].

Human infection by the adult tapeworm - *T. solium* taeniosis - causes only mild symptoms, such as abdominal pain or diarrhoea, if any [13]. Data on taeniosis prevalence in sub-Saharan Africa are still scarce. Cross-sectional studies conducted in rural communities have reported prevalence proportions of taeniosis using a copro-antigen-enzyme linked immunosorbent assay (copro-Ag-ELISA) of 19.9% in western Kenya, 6.3 to 11.9% in the Eastern Province of Zambia, and 1.1 to 5. 2% in Tanzania [14–18]. Moreover, a Tanzanian study conducted in Mbeya Rural District reported a taeniosis-antibody (Ab) prevalence of 4.1% using a rES38-immunoblot [17].

Many *T. solium* endemic areas in sub-Saharan Africa are also endemic for the human immunodeficiency virus (HIV) [19]. Nearly 25 million people are estimated to live with HIV/acquired immunodeficiency syndrome (AIDS) in sub-Saharan Africa [20]. While an overall decline in HIV/AIDS prevalence is observed in most African countries, the incidence of HIV is increasing in some rural areas [21] - most of them resource-poor - where *T. solium* has also been reported [12, 19]. This suggests the presence of co-infections in several predisposed countries. However, while HIV has been shown to interact with tuberculosis, malaria and some soil-transmitted parasitic infections [22–24], much less is known about how HIV modifies the manifestations of NCC. Not only may HIV modify clinical manifestations, but it may also impact the interpretation of sero-diagnostic results and required treatment schemes for NCC and taeniosis [25, 26]. Some authors have suggested that patients with higher $CD4^+$ T-lymphocyte ($CD4^+$) counts are more likely to develop symptomatic NCC needing treatment, whereas patients with advanced HIV and lower $CD4^+$ counts present either asymptomatically or atypically (giant and racemose cysts) [27–30]. In contrast, in a cross-sectional study conducted among HIV+ people in Mozambique, no significant correlation was found between presence of CC-Ab and $CD4^+$ counts [31]. The hypotheses that HIV+ individuals with low $CD4^+$ counts are more likely to develop symptomatic NCC was not supported in another study [32]. A Mexican autopsy study showed that NCC was even less common in people with HIV (1.1%) than among people without HIV (2.4%) [33], whereas in South-Africa, NCC has been described as one of the most present focal brain lesions in people with HIV/AIDS presenting with neurological signs [30]. In addition to seemingly unpredictable NCC manifestations in people with HIV/AIDS, highly active antiretroviral therapy (HAART) may lead to activation of latent NCC in the context of an immune reconstitution inflammatory syndrome with potentially deleterious effects for the affected individual [32, 34].

Based on the above controversy, the aim of this study was to estimate the prevalence of and factors associated with *T. solium* infections (taeniosis, CC, and NCC) among HIV+ and HIV− individuals in northern Tanzania.

Methods

Study sites

HIV positive (HIV+) individuals were recruited at the HIV Care and Treatment Centre (CTC) of HLH in Haydom, Mbulu district, Manyara region, northern Tanzania. HLH is a 429 bed-hospital serving around 15 400 inpatients and 70 150 outpatients per year [35]. As of December 2012, 1 898 HIV patients had sought care at the CTC clinic. All HIV/AIDS-related investigations and treatment are free of charge to the patient according to the Tanzanian National Policy on HIV/AIDS care and treatment. The villages of residence of the HIV+ patients were used to sample match HIV− individuals. These villages were located in the Mbulu, Hanang and Babati districts of the Manyara region and Iramba district of the Singida region (Fig. 1). All study districts were characterized by poor infrastructure and

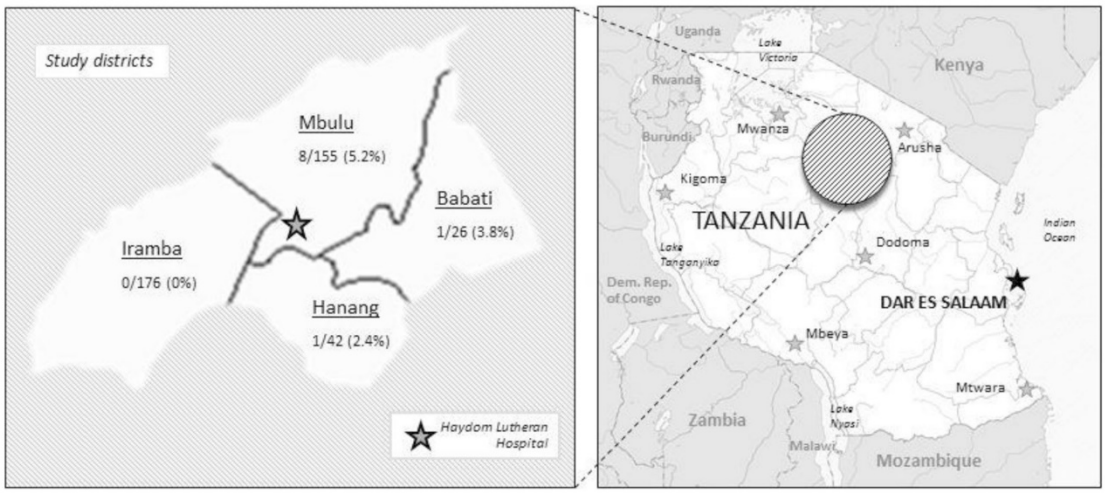

Fig. 1 Map of study area and distribution of identified TSOL+ individuals of the initially recruited study population with known origin and serology ($n = 399$)

living conditions, lack of sanitation, and farming as the main source of income. In 2008, the Manyara region reported that 19.6% of rural households reared pigs with the largest number of pigs found in the Mbulu district (51 198 pigs, 53.1% of the pig population in the Manyara region), followed by the Babati district (19 587 pigs, 20.3%) and the Hanang district (15 310 pigs, 5.9%) [36]. The Iramba district reported 42 073 pigs, which corresponds to 86% of the total pig population in the Singida region [37].

According to the Tanzania HIV/AIDS and Malaria Indicator Survey (THMIS) 2011-12 [38], the overall HIV prevalence in Tanzania was estimated to be 5.1% among adults aged 15–49 years (6% among women, 4% among men) during our study period. In the same report, prevalence proportions of 1.5% for the Manyara region and 3.3% for the Singida region were estimated. It is believed that HIV emerged in these regions relatively late (mid 1990s), but has steadily increased ever since and already reached the country's average in some districts like Babati [39].

Study design and study population

A cross-sectional study was conducted among 170 HIV+ and 170 age (+/− 10 years), gender and village of residence-matched HIV− individuals. The rationale for matching was to limit variation in exposure to *T. solium* eggs among HIV+ and HIV− participants. Participants were recruited from January 2011 to February 2013. Every day, HIV+ patients attending CTC for regular clinical check-ups and/or HAART were invited to participate in the study. Age, gender and village of residence of each consenting HIV+ patient were entered into an Excel sheet on a daily basis. For the age range of the individual matching partner a range of +/− 10% (with minimum and maximum target age) was calculated. Following this list, a field team including one nurse from CTC and one research assistant went each day to the appropriate villages to identify matching HIV− participants. With the help of village headmen/headwomen and local helpers, potential candidates were visited at their homes and asked to voluntarily participate in this study. The overall recruitment was stopped when a total of 433 participants, resulting in 170 matching pairs, had been identified (Fig. 2). Initial HIV testing of individuals enrolled in CTC was performed using two rapid Ab-tests according to the Tanzanian national algorithm for HIV testing: Alere Determine HIV-1/2 (Abbott laboratories, Abbott Park, IL, USA) and Uni-Gold™ Recombigen® HIV-1/2 (Trinity Biotech, USA). In the case of a positive reading in the Alere Determine HIV-1/2 test the serum sample was subjected to the second rapid Ab-test: Uni-Gold™ Recombigen® HIV-1/2 test. Concordant positive results were interpreted as positive for HIV-Ab. Discordant results were interpreted as inconclusive and the sample was sent to the regional hospital for confirmatory test using two ELISA tests: Enzygnost anti-HIV 1 + 2 Plus ELISA (Behring, Marburg, Germany) and Well-coenzyme HIV recombinant ELISA (Murex, Dartford, England). In this study, HIV− individuals were defined as participants who tested negative using the Alere Determine HIV-1/2 test and HIV+ individuals as participants tested positive following the algorithm described above. Clinical staging of

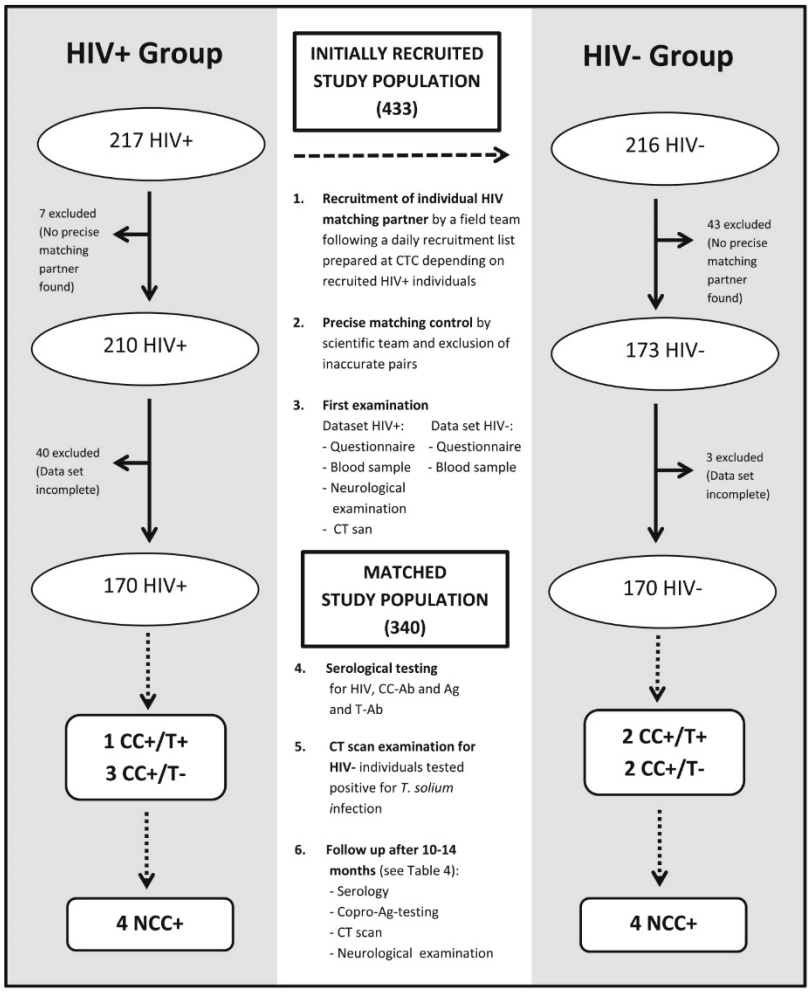

Fig. 2 Flow chart of the initially recruited and matched study populations. HIV: human immunodeficiency virus, CT: computed tomography, CC: cysticercosis, T: taeniosis, NCC: neurocysticercosis, Ab: antibody; Ag: antigen

HIV/AIDS was performed according to the revised World Health Organization (WHO) guidelines and HAART treatment status of all HIV+ was noted [40]. Most HIV+ participants (164 or 96%) were receiving HAART and none were under epilepsy or anti-inflammatory treatment at the time of recruitment. For ethical reasons, only individuals aged at least 9 years old were included in the study. Pregnant women were excluded from the study.

Consenting individuals were invited to answer a questionnaire, to undertake a clinical examination and to provide a blood sample for serological testing for taeniosis and CC. Neuroimaging was offered to all HIV+ participants and to only those HIV– participants positive to TSOL serology for ethical reasons.

Blood sample collection and laboratory testing

After counselling by a specially trained nurse, 10 ml of whole blood was collected by venipuncture from each participant. HIV+ and HIV– individuals were informed about the HIV test results immediately thereafter. $CD4^+$ counts were determined for all HIV+ patients using a fluorescent activated cell sorter machine (FACScount™, BD Biosciences, US) at the central laboratory of HLH. Blood samples from HIV– individuals were transported in cool boxes to the laboratory and immediately placed into refrigerators until required for further processing. Blood from HIV+ individuals was refrigerated in the HLH central laboratory immediately after drawing. After 1 to 6 h, serum was separated and stored at −20 °C until

serological testing for TSOL was performed. On average, two vials with 2 ml of serum were obtained from each individual. Four to twelve months later, samples were shipped to the CDC in Atlanta, USA, for further analyses and one safety back up sample remained at the Parasitology Laboratory of MUHAS to avoid total loss in case of any damage to the sample during the long shipment. Two tests were used to detect the presence of Ab to CC (LLGP-EITB and rT24H-immunoblot), one test was used to detect the presence of antigen (Ag) to CC (Ag-ELISA) and one test was used to detect the presence of Ab to taeniosis (rES33-immunoblot). LLGP-EITB is an enzyme-linked immunoelectrotransfer blot that detects CC-specific Ab to any of seven glycoproteins [41, 42]. The rT24H-test is an immunoblot method that detects CC-specific Ab to a *T. solium* recombinant Ag [43]. The Ag-ELISA that detects *Taenia*-Ag in serum is a monoclonal Ab (B158/B60 Ab) based capture ELISA and was performed following the modified protocol described by Dorny et al. [44]. The rES33-test is an immunoblot method that detects adult *T. solium* specific Ab using a recombinant protein derived from the excretory-secretory proteins of the adult tapeworms [45, 46]. Ab to both of the recombinant peptides, rT24H and rES33, were assessed in the same test. All test results were interpreted independently and blinded by two scientists with many years of experience in reading these *T. solium* in-house tests. For quality assurance each positive test was repeated at least once as well as 15% randomly selected negative samples.

Definitions

T. solium positive individuals (TSOL+) were defined as those with a positive result in at least one of the four serological tests described above while those negative in all tests were considered *T. solium* negative (TSOL–). Positive CC cases were defined as those individuals positive to the LLGP-EITB, rT24H-immunoblot or Ag-ELISA test. Taeniosis cases were defined as individuals positive to the rES33-immunoblot test. NCC cases were defined following the revised criteria of Del Brutto [10]. Viable cysts (active NCC) were defined as cystic lesions (with or without visible scolex) or lesions with ring enhancement. Calcified cysts (inactive NCC) were defined as hyperdense lesions with no sign of ring enhancement [47].

Neuroimaging

All HIV+ individuals underwent CT examination at baseline in a Toshiba Auklet Single Slice Spiral CT machine at HLH. HIV–/TSOL+ participants received their CT examination at the Aga Khan Health Centre in Arusha since the CT machine at HLH did not work at the time of the follow-up examinations. All follow-up CT scans of HIV+/TSOL+ were also performed in Arusha for the same reason. This health center used a Siemens Somatom Emotion CT machine. Both machines provided 5 mm slices and took 64 slices per picture. Intravenous contrast medium was used in all patients. CT scan images were evaluated by the local radiologists and sent to the Department of Neurology at the Technical University Munich (TUM) for a second blinded evaluation by a neurologist specialized in NCC diagnoses.

Research questionnaire

Each participant was asked to answer a socio-demographic and a medical history interview questionnaire. Interviews with HIV+ individuals were performed by a clinical officer at the CTC clinic and with HIV– individuals by a trained nurse in their villages of residence. The study nurses delivered the questionnaires at the CTC clinic. The questionnaire was adapted from a previous validated questionnaire used by the *Cysticercosis Working Group in Eastern and Southern Africa (CWGESA)* and addressed socio-demography, pork consumption habits as well as hygiene and sanitary practices [48]. Questions with an emphasis on self-reported past and present neurological disorders, such as acute and chronic headaches, peripheral nervous system (PNS) and CNS signs and symptoms including epileptic seizures as well as psychiatric disorders were included; so were questions on family history of neurological disease. HIV+ individuals were also asked about their past HIV history including opportunistic infections, HAART duration as well as compliance, amongst others. The questionnaire was developed in English, translated into Swahili and back-translated to English by two independent people. A standard neurological examination was performed on all HIV+ individuals by a medical doctor specializing in neurology.

Follow-up of seropositive individuals

Ten to fourteen months elapsed between sampling and receipt of the serological tests results due to logistical reasons and challenges in tracing patients, therefore HIV+/TSOL+ participants were invited for a second CT scan and blood collection (10 ml from each individual) so that appropriate treatment could be provided. This second clinical examination and follow-up CT scan were performed shortly before treatment and blood samples were taken at HLH. Participants identified HIV–/TSOL+ were invited for their first CT scan and neurological examination, and second blood drawing before treatment. Taeniosis positive participants were treated with niclosamide and symptomatic NCC cases with albendazole and dexamethasone. Present $CD4^+$ counts of HIV+ individuals were obtained and all serum samples were again shipped to the CDC in Atlanta for testing as described above. In addition, before treatment, TSOL+ participants were asked to provide three stool samples for copro-Ag-ELISA

testing at the CDC, following a protocol described by Guezala et al. [49]. Due to financial limitations in our study copro-Ag testing could only be performed during follow-up.

Statistical analysis

Analysis of associations between potential risk factors including HIV (independent variables) and TSOL (dependent variable) was performed by bivariate approximative tests (χ^2-tests) and exact tests (Fisher's tests) using Epi Info, version 3.3.2 (CDC, Atlanta, GA). Significant differences were defined as p-values below 0.05. McNemar tests were used for the paired analysis associations between the HIV status and TSOL, as well as for determining all the neurological outcomes. Matched prevalence proportion ratios (mPPR) and their 95%*CI* were obtained using the csmatch command in Stata 14.0. Statistical significance of associations between HIV and other factors among all matched and unmatched recruited participants and among the HIV positive group were evaluated using the chi-square test for categorical variables and the Kruskal Wallis tests for continuous variables. Matched analyses were performed using Stata 14.0.

Results

Demographic characteristics of HIV+ and HIV– individuals of the matched study population

Initially, 217 HIV+ individuals at CTC and 216 HIV– individuals were recruited to participate in the study. The initial aim of this recruitment was to identify a minimum of 150 matched pairs of HIV+ and HIV– individuals. After the initial recruitment, 40 HIV+ and three HIV– individuals were excluded due to a loss of follow-up or because the individual refused to participate further in the study. Full data sets comprised a completed questionnaire, serological results as well as at least one cranial CT examination and, for HIV+ participants, a neurological examination. After applying the matching criteria, seven additional HIV+ individuals and 43 HIV– individuals were excluded from the group of 177 HIV+ and 213 HIV– individuals, resulting in 170 matching HIV+/HIV– pairs available for analysis (Fig. 2).

The socio-demographic characteristics of the matched groups are reported in Table 1. As determined by the design, each group was 50% male and the median age was 39 years and 40 years in the HIV+ and HIV– matched participants groups, respectively. The most frequent tribe was Iraqw (42.6%), followed by Nyiramba (35.6%), Nyisanzu (8.5%) and other tribes (13.2%). Most of study participants lived in the Iramba district (45.6%), followed by the Mbulu (38.5%), Hanang (10.9%) and Babati districts (5.0%) (Table 1).

Table 1 Demographic characteristics of HIV+ and HIV– individuals of the matched study population

Variables	HIV+ (170)		HIV– (170)		Total (340)		*p*-value
	n	%	*n*	%	*n*	%	
Gender							1.00[a]
Male	85	50.0	85	50.0	170	50.0	–
Age group							0.50*
9–19 years	5	2.9	6	3.5	11	3.2	0.61*
20–39 years	70	41.2	82	48.2	152	44.7	0.23*
40–59 years	83	48.8	72	42.4	155	45.6	0.12*
60–74 years	12	7.1	10	5.9	22	6.5	0.88*
District							0.96*
Mbulu	62	36.5	69	40.6	131	38.5	0.44*
Iramba	82	48.2	73	42.9	155	45.6	0.33*
Hanang	18	10.6	19	11.2	37	10.9	0.86*
Babati	8	4.7	9	5.3	17	5.0	0.80*
Tribe							0.30
Iraqw	66	38.8	79	46.5	145	42.6	0.15
Nyiramba	64	37.6	57	33.5	121	35.6	0.43
Nyisanzu	13	7.6	16	9.4	29	8.5	0.56
Other tribes	27	15.9	18	10.6	45	13.2	0.15
Marital status							0.10
Married	130	76.5	143	84.1	273	80.3	0.08
Single	37	21.8	24	14.1	61	17.9	0.07
Divorced	3	1.8	3	1.8	6	1.8	1.00
Education							0.01
School not attended	37	21.8	18	10.6	55	16.2	–
School attended	133	78.2	152	89.4	285	83.8	–
Occupation							0.02
Peasant	149	87.6	155	91.2	304	89.4	0.53
Housewife	6	3.5	0	0.0	6	1.8	0.01
Business man/woman	3	1.8	0	0.0	3	0.9	0.08
Medical occupation	1	0.6	5	2.9	6	1.8	0.10
Student	6	3.5	1	0.6	7	2.1	0.06
Other	5	2.9	9	5.3	14	4.1	0.28

HIV human immunodeficiency virus
*The factors gender, age group, and district were considered for matching between HIV+ and HIV–

HIV related characteristics

At the time of recruitment 161 of 170 HIV+ individuals were on regular HAART therapy, three had discontinued treatment during recent years at least once, and six had not yet started HAART. The most commonly used HAART drugs were the first-line combinations lamivudine/zidovudine or lamivudine/stavudine/nevirapine (76.5%). 46 (27.1%) HIV+ patients reported opportunistic infections in the past year, mostly pulmonary

tuberculosis and other respiratory diseases as well as herpes zoster and other infectious skin diseases. The distribution of HIV/AIDS stages at the time of recruitment was: stage I: 71.8%, stage II: 9.4%, stage III: 16.5%, and stage IV: 2.4%.

Association between HIV and relevant past medical/neurological history, current neurological deficits, and TSOL risk factors among the matched pairs

HIV+ patients had significantly more history of acute headaches (mPPR: 2.38; 95%*CI*: 1.44–3.93) and a past history of psychiatric disorders (mPPR: 2.50; 95%*CI*: 1.02–6.15) than their HIV− counterparts. HIV+ individuals also tended to have more current overall neurological deficits (mPPR: 7.00; 95%*CI*: 0.86–56.89) and, specifically, peripheral neurological deficits (like anesthesia and hypoesthesia of legs and arms) (mPPR: 2.60; 95%*CI*: 0.93–7.29), but the difference was not significant (Tables 2 and 3).

Among the 164 pairs with this information available, HIV+ participants reported consuming pork significantly less often than HIV− participants (mPPR: 0.85; 95%*CI*: 0.75–0.96), but most of those consuming pork reported to eat pork less than once a month and only properly cooked. Only 1.2% of all study participants reported ever seeing cysts in pork. Of all matched study participants, 97.9% reported having access to latrines at home, and 98.2% of those reported always using the latrine. Only 9.4% of the participants reported washing hands before food consumption; the HIV+ participants tended to wash their hands less often than the matched HIV−

Table 2 Matched prevalence proportion ratios (mPPR) and their 95%*CI* for risk factors of TSOL, relevant past medical/neurological history and current neurological deficits

Factor (total number of pairs with data available)	Number of pairs				mPPR (95%*CI*)
	HIV+ w f/HIV− w f	HIV+ w f/HIV− wo f	HIV+ wo f/HIV− w f	HIV+ wo f/HIV− wo f	
History of overall headaches (162)	8	36	12	114	2.20 (1.39–3.48)
History of acute headaches (170)	7	31	9	123	2.38 (1.44–3.93)
History of chronic headaches (170)	0	6	4	160	1.50 (0.42–5.32)
Past or present epileptic seizures (170)	0	2	1	167	2.00 (0.18–20.06)
Current CNS symptoms (170)	0	7	1	162	7.00 (0.86–56.89)
Current PNS symptoms (164)	0	7	5	152	2.60 (0.93–7.29)
Any positive test for TSOL (170)	0	4	4	162	1.00 (0.25–4.00)
Positive for CC-Ag	0	1	0	169	Undefined
Positive for CC-Ab (170)	0	4	4	162	1.00 (0.25–4.00)
Positive for taeniosis-Ab (168)	0	3	2	163	0.50 (0.05–5.51)
Consumes pork (164)	95	18	38	13	0.85 (0.75–0.96)
Consumes undercooked pork (170)	0	9	10	151	0.90 (0.37–2.21)
Consumes pork at least once a month (170)	3	19	20	128	0.76 (0.42–1.38)
Has seen cysts in pigs (170)	0	3	1	166	3.00 (0.31–28.84)
Has access to a latrine (170)	163	2	5	0	0.98 (0.95–1.01)
History of tapeworm carrier in family (170)	1	6	2	161	2.33 (0.70–7.82)
Handwashing before eating (170)	0	11	20	139	0.55 (0.26–1.15)
Anthelminthic treatment in the past year (170)	3	10	20	137	0.57 (0.30–1.05)

mPPR matched prevalence proportion ratio, *CI* confidence interval, *HIV* human immunodeficiency virus, *w* with, *wo* without, *f* factor, *CNS* central nervous system, *PNS* peripheral nerval system, *TSOL T. solium* taeniosis/cysticercosis, *CC* cysticercosis, *Ag* antigen

Table 3 Past neurological history, public health and diagnostic data of HIV+ and HIV– individuals of the matched study population

Variables	HIV+ (170)		HIV– (170)		Total (340)		*p*-value
	n	%	*n*	%	*n*	%	
History of acute headaches							
Yes	38	22.4	16	9.4	54	15.9	*<0.01*
History of chronic headaches							
Yes	6	3.5	4	2.4	10	2.9	0.52
Past or present epileptic seizures							
Yes	4	2.4	3	1.8	7	2.1	0.70
History of psychiatric disorders							
Yes	15	8.8	6	3.5	21	6.2	*0.04*
Current CNS symptoms							
Yes	7	4.1	1	0.6	8	2.4	*0.03*
Current PNS symptoms							
Yes	13	7.6	5	2.9	18	5.3	0.05
CC-Ag							
Positive	1	0.6	0	0.0	1	0.3	0.32
CC-Ab by LLGP-EITB							
Positive	4	2.4	4	2.4	8	2.4	1.00
CC-Ab by rT24H-blot							
Positive	4	2.4	4	2.4	8	2.4	1.00
Taeniosis-Ab							
Positive	1	0.6	2	1.2	3	0.9	0.56
NCC[a]							
Positive	4	2.4	4	2.4	8	2.4	1.00
History of tapeworm carrier in family							
Yes	7	4.1	3	1.8	10	2.9	0.20
Handwashing before eating							
Yes	12	7.1	20	11.8	32	9.4	0.14
Anthelmintic treatment in the past year							
Yes	12	7.1	25	14.7	37	10.9	*0.02*

CNS central nervous system, *PNS* peripheral nervous system, *HAART* highly active antiretroviral therapy, *CC* cysticercosis, *Ag* antigen, *Ab* antibody, *LLGP-EITB* lentin-lectin glycoprotein electroimmunosorbent blot, *NCC* neurocysticercosis

[a]According to the revised diagnostic criteria proposed by Del Brutto [10]

participants (mPPR: 0.55; 95%*CI*: 0.26–1.15) (Tables 2 and 3).

There were six pairs where the HIV+ individual reported living in a household with a member with a past history of tapeworm infection, while the HIV– matched participant did not; in only two pairs did the HIV– participant reported such history and the HIV+ did not (mPPR: 2.33; 95%*CI*: 0.70–7.82). Fewer HIV+ participants tended to report anthelminthic treatment in the past than the matched HIV– participants (mPPR: 0.57; 95%*CI*: 0.30–1.05), but the difference was not significant (Tables 2 and 3).

Distribution of TSOL tests results among the matched pairs and in the initially recruited population

There was no association between HIV and TSOL in this population with four discordant pairs each of HIV+/TSOL+ with HIV–/TSOL– and HIV+/TSOL– with HIV–/TSOL+ (mPPR: 1.0; 95%*CI*: 0.25–4.00). This corresponds to an overall prevalence of 2.4% (95%*CI*: 0.6–5.9) of TSOL among both HIV+ and HIV– participants. Comparing detailed test results, no significant differences were observed between matched HIV+ and HIV– individuals regarding the sero-prevalence of taeniosis-Ab (mPPR: 0.5; 95%*CI*: 0.05–5.51), CC-Ab (mPPR: 1.0; 95%*CI*: 0.25–4.00), and CC-Ag (mPPR undefined because there was only one discordant pair with HIV+ positive to the Ag-ELISA and HIV– negative to Ag-ELISA) were detected (Fig. 2, Tables 2 and 3).

Of the 404 participants initially recruited with sera available, which include the 340 matched participants, the prevalence of CC-Ab was 2.5% (95%*CI*: 1.2–4.5). For more clinical, serological and risk factor data of those 10 TSOL+ individuals refer to Additional file 2: Table S1. The prevalence of Ab to taeniosis was 1.2% (95%*CI*: 0.4–2.9). All five of 404 rES33 positive individuals also had Ab to CC-Ag or positive Ag-results. Only three (0.7%; 95%*CI*: 0.4–2.9) participants were positive for the presence of CC-Ag. The prevalence of TSOL was slightly higher among those presenting with headaches or seizures (3.7%; 95%*CI*: 0.8–10.4) than among those without such symptoms (2.2%, 95%*CI*: 0.9–4.4), but this difference was not statistically significant (Tables 2 and 3).

The district of origin and serological results were available for 399 out of 433 initially recruited individuals. The prevalence proportion of TSOL was considerably higher among participants living in the Mbulu district (5.2%, 95%*CI*: 1.9–10.4) than in other districts (0.8%; 95%*CI*: 0.1–2.8) (Fig. 1), a difference which was statistically significant ($p = 0.008$) (Table 1).

Association between $CD4^+$ counts, HIV stages, HAART and TSOL

There were only four HIV+ participants positive for any TSOL test. Median $CD4^+$ counts of the four HIV+/TSOL+ individuals were 358 cells/μl (range 170 to 554) while it was 399 cells/μl (range 9 to 1 878) among the 166 HIV+ participants of the matched population negative to all TSOL tests ($p = 0.88$). Of four HIV+/TSOL+, three individuals were classified in HIV stage I and one in stage III, a distribution similar to that found in those with all TSOL tests negative ($p = 0.88$). All four HIV+/TSOL+ individuals had been receiving HAART for 4 years or less (Table 4).

Table 4 Radiological and serological results of TSOL+ individuals of the matched and initially recruited population

	P 1	P 2	P 3	P 4	P 5	P 6	P 7	P 8	P 9	P 10
Matched study group	yes	yes	yes	yes	yes	yes	yes	yes	no	no
Age	50	46	45	60	46	28	27	51	38	14
Gender	f	m	m	m	m	f	f	m	m	m
First clinical examination										
HIV parameters										
HIV status	+	+	+	+	-	-	-	-	-	-
HIV stage	I	I	I	III	-	-	-	-	-	-
HAART drugs	ZDV/3TC/EFZ	ZDV/3TC/EFZ	ZDV/3TC/EFZ	ZDV/3TC/EFZ	-	-	-	-	-	-
HAART treatment since (years)	<1	3	3	4	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
NCC symptoms/signs	-	-	-	headaches	-	severe headaches	-	-	epi	epi, enc[a]
CT diagnosis										
Calcified cysts	+	-	+	+	o	o	o	o	+	-
Viable cysts	-	-	-	-	o	o	o	o	-	+
Other NCC relevant findings	-	-	-	-	o	o	o	o	-	hydrocephalus
Laboratory diagnosis										
$CD4^+$ counts	554	433	276	170	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
CC- Ab	+	+	+	+	+	+	+	+	+	+
CC-Ag	-	-	-	+	-	-	-	-	-	+
Taeniosis-Ab	+	-	-	-	-	-	+	+	+	+
Second clinical examination										
NCC symptoms/signs	x	x	-	-	-	severe headaches	-	x	d	epi, enc[a]
CT diagnosis								x		
Calcified cysts	x	x	+	+	+	-	+	x	d	+
Viable cysts	x	x	-	-	-	-	-	x	d	+
Other NCC relevant findings	x	x	-	-	-	hydrocephalus[b]	-	x	d	hydrocephalus
Laboratory findings										
$CD4^+$ counts	521	400	368	184	n.a.	n.a.	n.a.	n.a.	d	n.a.
CC-Ab	+	+	-	-	+	x	x	x	d	x
CC-Ag	-	-	-	+	-	x	x	x	d	x
Taeniosis-Ab	+	-	-	-	-	x	x	x	d	x
Taeniosis-copro-Ag	-	-	-	-	-	-	-	x	d	x

P patient number, *m* male, *f* female, *HIV* human immunodeficiency virus, *HAART* highly active antiretroviral therapy, *ZDV* zidovudine, *3TC* lamivudine, *EFZ* efavirenz, *NCC* neurocysticercosis, *epi* epilepsy, *enc* encephalopathy, *CT* computed tomography, *$CD4^+$* $CD4^+$ T-lymphocyte cell counts, *n.a.* not applicable, because in the group of HIV– these parameters were not tested and no HAART was taken, *CC* cysticercosis, *Ab* antibodies, *Ag* antigen, + positive, – negative, *o* was not taken at once due to ethical concerns of performing a CT scan in healthy individuals, but was offered when the positive test serology was confirmed, *x* patient refused or was not found, *d* patient died before 2^{nd} examination with unclear diagnosis (strong headaches and abdominal pain reported before death)

[a]Patient was unconscious with signs of brainstem involvement and generalized increased muscle tone leading to flexion contractures of all four limbs, most likely in the context of increased intracranial pressure

[b]Mass in 4^{th} ventricle causing obstructive hydrocephalus

Radiological and serological results of TSOL+ individuals among the matched pairs and initially recruited population

Details on the four HIV+ patients (P1-P4) and the four HIV– patients (P5-P8) who were also TSOL+ in addition to two HIV– participants (P9-P10) who could not be matched but were TSOL+ (initially recruited study population; Fig. 2) are provided in Table 4. More clinical details on these ten patients are shown in Additional file 2: Table S1.

Overall, all four HIV+/TSOL+ and three of four HIV–/TSOL+ participants of the matched study population agreed to have at least one CT scan at the time of

their first and second clinical examination. The two unmatched HIV−/TSOL+ individuals (P9, P10) received a CT scan at their first clinical examination due to the severe clinical condition they were in (epilepsy, encephalopathy). None of the 166 HIV+/TSOL− participants presented with brain lesions compatible with NCC, but three (P1, P3 and P4) of the four HIV+/TSOL+ had definitive NCC. The fourth participant did not show any lesions in the brain (P2). This would suggest an overall specificity of 99.4% (95%*CI*: 96.7–100) of the CC tests (Ag-ELISA, LLGP-EITB, rT24H-immunoblot) to detect NCC among the HIV+ patients in this population. There were too few cases to estimate the sensitivity with any precision. Overall, there was perfect agreement between the EITB and rT24H for the detection of Ab to CC (Tables 3 and 4).

Among the three matched HIV−/TSOL+ participants with CT scan results, two were found to have definitive NCC (P5, P7) and one other had probable NCC (P6). The latter presented with an obstructive hydrocephalus and a mass in the 4th ventricle. Among all HIV− participants positive to TSOL and receiving neuroimaging, four out of five had lesions of NCC, suggesting that, although there were only small numbers, HAART may not impact on the proportion of NCC among those positive for CC in people with HIV/AIDS. The proportion of NCC was therefore 1.8% among the matched HIV+ participants, but cannot be estimated in the matched HIV− participants since only three had a CT scan.

Among the seven NCC cases, five presented with calcified lesions without perilesional edema and were free of any viable cysts. Among the two unmatched HIV−/NCC participants, one was found to have multiple viable cysts in the parenchyma, some of them with perilesional edema (P10), and the other had several calcified cysts (P9). The number of detected lesions per NCC case in this study ranged from one to ten, except in P10, where more than 20 active lesions could be identified. No lesions outside the parenchyma were detected (Table 4).

Description of symptoms among patients with NCC

Four (1 HIV+, 3 HIV−) of eight participants with definitive or probable NCC presented with neurological symptoms. Two of the symptomatic participants presented with headaches (1 HIV+ with acute and 1 HIV− with chronic headaches) and two HIV− individuals with epilepsy. One HIV− participant (P10), a boy aged 14 years, was unconscious at the time of admission to HLH with signs of brainstem involvement and generalized increased muscle tone leading to flexion contractures of all four limbs, most likely in the context of increased intracranial pressure. P10 was the only participant with positive serological results for all tests (CC-Ab, CC-Ag and taeniosis-Ab). The CD4$^+$ counts of the only symptomatic (presenting with acute headaches) HIV+ individual (P4) was 170 cells/μl, the lowest level of the four HIV+ individuals who were positive to TSOL (Table 4).

Follow-up of TSOL+ individuals

Of the ten participants found positive to TSOL at baseline, three were lost to follow-up, including one unmatched HIV− participant who died for unclear reasons (strong headaches and abdominal pain reported before death). Five (4 HIV+ and 1 HIV−) of the seven followed participants provided sera and six (4 HIV+ and 2 HIV−) provided a stool sample. Seven (4 HIV+ and 3 HIV−) participants had a stool examination at the time of follow up, but all of them had a negative copro-Ag-ELISA test result. The only HIV+ participant positive to rES33 at baseline was still positive at follow-up. Among the five participants positive to CC at baseline, one HIV+ participant became sero-negative to the tests detecting Ab. Interestingly, this participant (P3) had an increase of 92 cells/μl in CD4$^+$ (from 276 to 368 cells/μl; increase of 33% from baseline), in contrast to the three other HIV+ participants for whom the CD4$^+$ counts decreased slightly or remained similar. Only three participants accepted to undergo a second CT examination. Two of them did not show any changes, whereas P10, who had shown several viable cysts on the first CT scan, revealed mostly calcifications as well as a few viable cysts. This young (14-year-old) patient was hospitalized and, after serological and radiological confirmation, received anti-inflammatory (dexamethasone) and anthelminthic (albendazole, niclosamide) treatments repeatedly during the whole study period. There were no major improvements in the symptoms after treatment and the patient was transferred to a home for children with special needs after the study. Overall, there was no change in the clinical presentation of all the TSOL+ individuals at follow-up. None of the asymptomatic NCC cases reported new clinical signs/symptoms (Table 4, Additional file 2: Table S1).

Discussion

TSOL has only been investigated patchily with contradictory results in people living with HIV/AIDS and the impact of CD4$^+$ counts, HAART duration and HIV stages on the incidence of *T. solium* and the exacerbation of NCC have not been explored so far. Depending on the endemicity of TSOL, between 10 and 20% of HIV+ individuals may also present with TSOL and/or suffer from NCC, but there are currently no recommendations for adequate case management in cases of co-infection [31]. This important gap for controlling TSOL/NCC has largely been overlooked. Our study matched HIV+ to HIV− participants by age, gender and village of residence to adjust for potential environmental contamination with eggs of *T. solium* and the

varying immunological response in relation to age and gender. To our knowledge, our study is the first to adjust for such factors in people living with HIV/AIDS and was designed to address these knowledge gaps. Unfortunately, the prevalence of taeniosis, CC and NCC was a lot lower than had been reported in the region by past studies [9, 17], and limited our ability to fully explore these questions with confidence.

We found a prevalence proportion of Ab to CC of 2.4% among the matched participants and of 2.5% in the initially recruited population, with no major differences between the HIV+ and HIV− participants. These prevalence rates of Ab to CC were similar to a 2.2% prevalence rate reported among healthy individuals in Kenya [50]. However, our estimate is much lower than that found in a study conducted at the same time in communities of the Mbulu district where a prevalence proportion of 16.3% was reported when using a commercially available Western blot test (LDBIO Diagnostics) [51]. When using data from all participants initially recruited, the prevalence of TSOL was highest in the Mbulu district (5.2%), and this was true among HIV+ and HIV− participants, but was still lower than that found by Mwang'onde et al. [51]. Possible explanation for these differences are the use of a different diagnostic test for the detection of Ab, possible selection bias of participants as no details on sampling is provided by the authors of a previous study [51], and possible clustering of CC in certain villages within the Mbulu district which was already described by Ngowi at al. [52]. Clustering of CC by villages in Africa has also been observed in pigs in the Mbulu district and in humans living in other countries [16, 52].

The prevalence of CC-Ag positive individuals in our study is also considerably lower than that found in other countries of southeastern Africa: Zambia (5.8%), Tanzania (16.7%), and the Democratic Republic of Congo (21.6%) [15–17, 53], and was lower than the overall prevalence of 7.3% for Africa presented in [54]. However, a study from Burkina Faso recorded varying proportions, from 0.0 to 11.5% in 60 villages, which partially supports our findings [55].

In our study, NCC was confirmed by serology and CT scan in about 2% of HIV+. In a study conducted in India, of 100 HIV+ serum samples two (2%) were detected with CC-Ab by EITB [56]. In Mexico, only 1.1% of NCC have been reported in a study among HIV/AIDS cases, compared with 2.4% in control autopsies [33]. Furthermore, a study conducted in Mozambique found a CC-Ab proportion of 10.2% in 601 HIV+ individuals by a commercial multiplex Western Blot IgG test for several parasites (LDBIO Diagnostics) [31].

Overall, it has to be considered that due to the matched design in this study and no use of a cross-sectional approach, obtained prevalence estimates have to be interpreted carefully. No cluster analysis could be performed for this reason too.

Four TSOL individuals, two matched individuals (1 HIV+, 1 HIV−) as well as two initially recruited individuals (2 HIV−) presented with neurological symptoms. Our results are limited by the fact that symptomatic NCC cases with a negative CC-Ab and CC-Ag titer and people with extraparenchymal or spinal lesions might have been missed. Ethical restrictions did not allow for further radiological follow-up of sero-negative HIV− participants and funds as well as logistics made the performance of magnetic resonance imaging (MRI) impossible.

Of all eight NCC cases identified in our wider study population four were classified as asymptomatic and four as symptomatic NCC cases. This correlates with findings of other studies that proposed that around 50% of NCC cases remain asymptomatic [4, 56]. The two reported neurological symptoms/signs were headaches and epilepsy, which is consistent with the main neurological presentations of NCC [2–4]. All asymptomatic NCC cases showed one to five intraparenchymal calcified lesions in the CT scan, and none of those followed up developed neurological symptoms 8 to 10 months later. This does not rule out that these individuals may become symptomatic in the future.

The prevalence of taeniosis-Ab in the initially recruited population was 1.2%, the first such estimate for northern Tanzania. However, this population is not representative of the community but was selected to match residence of HIV+ individuals receiving care at the HLH. Data on taeniosis-Ab are still scarce worldwide, mostly due to the unavailability of a commercial diagnostic test [57]. The rES33-immunoblot in-house assay has been reported to have a sensitivity of 98% and a specificity of 99% for the detection of the adult stage of *T. solium* in human intestines [45]. However, the presence of taeniosis-Ab only reflects exposure to the adult tapeworm and cannot differentiate past from present infections. Previous estimates of the prevalence of adult tapeworm infections measured with a copro-Ag-ELISA in endemic areas vary from 0.1 to 4.0% in community-based settings, with only one study from Zambia reporting a prevalence of 11.9% [13, 15–18]. In our study, all individuals with a positive taeniosis-Ab titer lived in the Mbulu district (Fig. 1). In addition to the possible natural clustering of TSOL, in contrast to the other districts, Mbulu had only recently started annual mass drug administration (MDA) of anthelminthic drugs which may have reduced the natural taeniosis prevalence.

Our analysis of factors for TSOL infection revealed that the HIV+ group reported washing their hands less often, was more exposed to people with taeniosis in their household but had taken fewer anthelminthic drugs in the past (as specifically prescribed treatment or in mass

drug administration initiatives). However, they also consumed less pork (Tables 2 and 3), so there could be a slight tendency that the HIV+ group may be slightly greater at risk of CC and a little less to taeniosis, based on known infection routes [2–4]. However, serological findings of our study could not support this hypothesis as in our study four HIV− individuals had a positive taeniosis-Ab titer in comparison to only one HIV+ individual.

In the present study, we could not detect any difference in the prevalence of taeniosis, CC and NCC between matched HIV+ and HIV− individuals. Our results are in accordance with that of Walson et al., who suggested that helminth prevalence in HIV+ individuals is similar to the general population prevalence in endemic settings [58], although others have found intestinal helminths - like *Strongyloides stercoralis* - to be more prevalent in HIV+ people [59, 60]. However, a clear drawback of our study was the seemingly low prevalence of TSOL in our overall study population and therefore differences between the HIV+ and HIV− individuals may have gone unnoticed. Furthermore, there was no difference in the presence of CC-Ab between matched HIV+ and HIV− individuals. A reduced production of Ab against protozoans such as *Toxoplasma gondii* has been discussed in HIV+ individuals, as well as the possible failure of serological diagnostic tests to detect these co-infections in severely immunocompromised individuals [61]. In our study, CC-Ab positive HIV+ individuals had moderately reduced to normal $CD4^+$ counts and were probably still immunocompetent enough to produce Ab. CC in HIV+ individuals, including Ab and/or Ag-positive individuals, was distributed equally (1/4) in the four groups of individuals with defined $CD4^+$ counts (group I: ≤200; group II: 201-350; group III: 351-500; group III: >500). Therefore, CC did not seem to be associated with $CD4^+$ counts in our study.

The single HIV+/NCC case with neurological symptoms presented with acute headaches, calcified cysts, $CD4^+$ counts of 170 cells/μl and was HIV stage III. All asymptomatic HIV+/NCC cases were HIV stage III. This result is in agreement with previous studies reporting symptomatic HIV+/NCC cases in individuals with $CD4^+$ counts <250 cells/μl [27, 32]. However, acute headaches in this case might also be linked to HIV infection, HAART, or reasons other than NCC.

Our results showing the absence of viable cysts or perilesional edemas lesions among HIV+/NCC cases are in contrast with a review of 27 HIV+/NCC cases with multiple parenchymal active lesions (viable cysts and enhancing lesions) as the most frequent radiological findings [32]. Beside genetic aspects, of the host and/or the parasite, and lower infection pressure the prevailing of cerebral calcifications in our HIV+ study population on the one hand may point towards a still functional immune system that is able to eliminate the parasite and on the other hand may be due to low infection pressure. Another reason might be that the HIV+/NCC cases acquired HIV after contracting TSOL.

Although this study was designed to allow similar levels of exposure to *T. solium* eggs in the HIV+ and HIV− groups, it had some important limitations which should be noted. First, the very small number of TSOL+ individuals in both the HIV+ and HIV− groups meant that we had very limited statistical power to identify any differences. Such result was surprising given that endemic levels of CC/NCC were recently reported in the same study area [9, 51].

Second, the vast majority of the HIV+ participants were receiving HAART, meaning that the impact of compromised immunological response usually associated with HIV on taeniosis, CC or NCC was diluted. An additional HIV+/HAART− group would have provided more detailed information on a possible influence of HAART (or the initiation of it) on the prevalence of T/CC/NCC and its clinical characteristics. However, recruitment of a sufficient number of HIV+ people that do not receive HAART was not possible within the study period due to national ethical reasons. So far, severe progressive and fatal NCC cases in HIV+ individuals were mostly described in patients who were not receiving HAART [7, 62, 63]. However, a recent cross-sectional study of a group of 601 HIV+ individuals conducted in Mozambique could not detect a difference in the presence of CC-Ab between HIV+ patients who were taking HAART and those who were not, nor was there a correlation between HAART duration and CC-Ab titers [31].

Conclusions

In conclusion, we did not detect any difference in prevalence and manifestation of taeniosis, CC and NCC between matched HIV+ and HIV− individuals in a TSOL endemic area of northern Tanzania. However, the herein presented data on TSOL/HIV co-infection obtained in a comparative study design are the first of its kind. This study clearly points out that further large-scale studies are urgently required to re-examine TSOL infection in HIV+ individuals and in patients who are and are not on HAART, as well as NCC progression in HIV+ individuals.

Additional files

Additional file 1: Multilingual abstracts in the six official working languages of the United Nations. (PDF 837 kb)

Additional file 2: Table S1. Clinical data, data on hygiene and eating habits, medication, family history and diagnostic data of TSOL+ individuals ($n = 10$) of the initially recruited study population. (DOC 74 kb)

Abbreviations
Ab: Antibody; Ag: Antigen; AIDS: Acquired immunodeficiency syndrome; CC: Cysticercosis; $CD4^+$: $CD4^+$ T-lymphocytes; CDC: Centers for Disease Control and Prevention; CI: Confidence interval; CNS: Central nerval system; CT: Computed tomography; CTC: HIV care and treatment centre; CWGESA: Cysticercosis Working Group in Eastern and Southern Africa; ELISA: Enzyme linked immunosorbent assay; HAART: Highly active antiretroviral therapy; HIV: Human immunodeficiency virus; HLH: Haydom Lutheran Hospital; IgG: Immunoglobulin G; LLGP-EITB: Lentin-lectin-glycoprotein-enzyme linked immunoelectrotransfer blot; mPPR: Matched prevalence proportion ratios; MRI: Magnetic resonance imaging; MUHAS: Muhimbili University of Health and Allied Sciences; NCC: Neurocysticercosis; NIMR: National Institute for Medical Research; P: Patient number; PNS: Peripheral nervous system; PWE: People with epilepsy; THMIS: Tanzania HIV/AIDS and Malaria Indicator Survey; TSOL: *Taenia solium* infection; TUM: Technical University Munich; WHO: World Health Organization

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Availability of data and materials
Raw data are available on request at any time.

Authors' contributions
Conceived and designed the projects: WM, HC and ASW. Performed the field survey and laboratory testing: VS, CK, JN, BN, DM. Contributed reagents and materials: PW, WM. Analyzed the data: VS, KHH, HC and ASW. Wrote the paper: VS. Reviewed the paper: CK, KHH, HC, BH, EN, JN, PW, DM, WM and ASW. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Ethics approval and consent to participate
Ethical approvals for this study were obtained from the Directorate of Research and Publications, Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam (Ref. No.: MU/DRP/REC/Vol.I/36, MU/RP/AEC/Vol.Xii/86 and MU/DRP/AEC/Vol.XVI/91) as well as from the Ethical Committee of Ludwig-Maximilians University (LMU) Munich, Germany. The project proposal and export permits for biological material to the USA were also cleared by the National Institute for Medical Research (NIMR), Tanzania, and a material transfer agreement with the Centers for Disease Control and Prevention (CDC), Atlanta, was obtained.
Risks and benefits of the diagnostic tests including computed tomography (CT) were explained to potential participants. Women who reported pregnancy or a missed period were excluded from this study. Following Tanzanian regulations, written informed consent was obtained from participants aged 18 years and over and oral assent from the patient as well as written consent from a parent was collected in case the patient was under 18 years old. In the event of illiteracy, forms were read out to the participant and fingerprints were taken. Before each HIV test, counselling by specially trained nurses from Haydom Lutheran Hospital (HLH) was performed. HIV+ and HIV− individuals were informed about the HIV test results immediately thereafter. In case of any pathological findings and required therapy, patients were transferred to the appropriate health units at HLH or other health facilities. Identified taeniosis carriers received free anthelminthic therapy (niclosamide) after serological results were available (around six months after sampling). All patients found positive for TSOL received intensive public health education regarding potential autoinfection, required hygiene and deworming to reduce the risk of new infection. Patients with epileptic seizures received symptomatic therapy until serological *T. solium* test results were available and decisions on further therapeutic steps could be made.

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