Article

Clinical characteristics and management of neurocysticercosis patients: a retrospective assessment of case reports from Europe

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Abstract:

Objectives: Neurocysticercosis (NCC) is a parasitic disease caused by the larval stage of the tapeworm *Taenia solium*. NCC mainly occurs in Africa, Latin America and South-East Asia and can cause a variety of clinical signs/symptoms. Although it is a rare disease in Europe, it should nonetheless be considered as a differential diagnosis. The aim of this study was to describe clinical characteristics and management of patients with NCC diagnosed and treated in Europe.

Methods: We conducted a systematic search of published and unpublished data on patients diagnosed with NCC in Europe (2000–2019) and extracted demographic, clinical and radiological information on each case, if available.

Results: Out of 293 identified NCC cases, 59% of patients presented initially with epileptic seizures (21% focal onset); 52% presented with headache and 54% had other neurological signs/symptoms. The majority of patients had a travel or migration history (76%), mostly from/to Latin America (38%), Africa (32%) or Asia (30%). Treatment varied largely depending on cyst location and number. The outcome was favorable in 90% of the cases.

Conclusions: Management of NCC in Europe varied considerably but often had a good outcome. Travel and migration to and from areas endemic for *T. solium* will likely result in continued low prevalence of NCC in Europe. Therefore, training and guidance of clinicians is recommended for optimal patient management.

Keywords: Neurocysticercosis; *Taenia solium*; Europe; neglected tropical diseases; NCC management; Global Health; Clinical epidemiology; One Health

INTRODUCTION

Neurocysticercosis (NCC) is caused by the tapeworm *Taenia solium*, a zoonotic parasite which has a pig-human-environment life cycle. Humans get NCC by ingesting parasite eggs, which are shed through feces of *T. solium* tapeworm carriers. Through environmental contamination and lack of hygiene these eggs can accidentally be ingested by humans. Once in the intestines, the larvae, which are released from eggs, cross the intestinal mucosa into the circulatory system through which they are transported to multiple organs, where they encyst (cysticerci). When these cysticerci affect the central nervous system (CNS), the disease is called NCC. Cysts can persist in the CNS for several years without causing any neurological signs/symptoms. Signs and symptoms are pleomorphic[1–4], often resulting from degeneration of the cysts and associated inflammatory host immune reaction. The most common neurological signs/symptoms are epileptic seizures, headache episodes, focal neurological deficits and signs of raised intracranial pressure.[1]

Neurological signs and symptoms depend on number, size, location (e.g. intraparenchymal or extraparenchymal and location within the brain parenchyma), and cyst stage. When located in the parenchyma, degeneration of cysts (colloidal and granular nodular stage) is associated with inflammation leading to perilesional oedema which can cause neurological signs/symptoms.[2,5]

Treatment options for intraparenchymal lesions include anthelmintic therapy with albendazole and/or praziquantel in combination with corticosteroids for vesicular cysts, or corticosteroids alone for degenerating cysts; both accompanied by anti-epileptic drugs, if necessary. For extraparenchymal lesions treatment options include ventriculoperitoneal shunting, or surgical removal of cysts.[4,6–13]

According to the distribution map for NCC published by WHO, Latin America, South and South-East Asia and sub-Saharan Africa are considered endemic.[14] In these areas, NCC accounts for around one third of all epilepsy cases.[4,15] In Europe, although data are scarce, the main countries affected are Spain, Portugal and Eastern European countries, however only rarely.[16–21] Until the 1990s, many autochthonous cases of *T. solium* infection were reported in Portugal and Spain.[16] To date, many immigrants who are likely to have been infected outside Europe are also diagnosed in these two countries.[16] In Eastern Europe, disease surveillance is only sporadic; a previous review reported a particularly large number of cases from Serbia with probable infection in Eastern Europe.

Disease presentation differs between world regions. While single enhancing intraparenchymal lesions are the predominant form of the disease in India, multiple lesions are common in Latin America which more commonly are also in the extraparenchymal space than in other world regions. For African populations, also multiple lesions which are mostly located in the parenchyma have been described.[2,22–25] For Europe, disease presentation has not yet been described.

Knowledge of diagnostic work-up and management of patients presenting with symptomatic NCC may be scarce among clinicians in Europe where NCC cases are rare and most clinicians have never seen a

NCC case.[26] As knowledge about differences of disease manifestation due to geographical characteristics or certain risk factors may help to correctly diagnose and treat patients, the aim of this study was to summarize and update information about clinical characteristics and management of NCC patients diagnosed in Europe.

METHODS

Systematic literature search: This project was part of CYSTINET (European Network on Taeniosis/Cysticercosis, COST Action TD 1302).[27] We conducted a systematic literature search of NCC case reports and case series, along with cases from the grey literature. Also reviewed were unpublished data collected via collaborating clinicians and laboratories. Moreover, experts familiar with NCC patient management in the European setting were consulted. The protocol for the conduct of systematic literature review followed the PRISMA-P outline and was registered on PROSPERO (registration number: CRD42016050729).[28] Ethical approval was obtained where required. Ethical approval for the retrospective analysis of anonymized patient data was granted by the ethics committee of the Klinikum rechts der Isar at the Technical University of Munich, Germany (208/16S).

Search methods: PubMed, EMBASE, Web of Science, Global Health (CABI), Global Index Medicus coupled with Aoister and Open Grey were searched for articles published between January 2000 to May 2019. Supplement Table S1 contains the precise search terms and dates. Moreover, each CYSTINET researcher searched for grey literature in their native countries (25 countries; the list of countries can be found under this link: http://www.cystinet.org/the-action/participating-countries/); references of included literature were evaluated for relevance and included if they met the inclusion criteria. No language restriction was applied; only studies on humans were included. (Systematic) reviews were screened for additional references.[16,17,19]

Study selection criteria: Inclusion and exclusion criteria were pre-defined in the study protocol (Supplement Table S2). Only data on NCC cases presenting in Europe (see list of included countries in Supplement Table S2) were included. Case reports and case series were considered for inclusion. NCC was defined as the presence of *T. solium* cysts/calcifications in the CNS confirmed on neuroimaging. Studies were excluded if 1) reporting on another *Taenia* species (e.g. *T. crassiceps, T. hydatigena, T. asiatica*), 2) reporting on cysticercosis only outside the CNS (e.g. muscles, eyes etc.), 3) reporting on patients treated outside Europe, 4) reporting year before 2000 (even if published after 2000), 5) reporting on the same patients (when reporting on the same patient both articles were taken into account for additional information, but the patient was counted as one) and 6) reporting on animals.

Study selection process: The Covidence online tool (https://www.covidence.org/) was employed to assess the published literature obtained from PubMed, EMBASE, Web of Science, Global Health (CABI),

and Global Index Medicus.[29] Literature was screened independently by four reviewers (AA, JB, PS, CU). Each selection required two votes from the reviewers; in the event of disagreement, a third reviewer was consulted. First, the titles and abstracts were screened and a decision was made whether to include or exclude the publication.

Next, publications were sorted by country name (Supplement Table S2), and if found suitable as per the inclusion criteria, retained. Following this, the complete texts of the papers were reviewed and the rationale for any exclusion specified. In order to confirm the validity and suitability of the inclusion/exclusion criteria, the procedure of study selection was test-run by all researchers. Searching Aoister and Open Grey in collaboration with CYSTINET members yielded grey literature, including doctoral theses, papers in languages other than English and conference abstracts[17,19], based on the same selection process as described above.

Collection of unpublished data: Attendees at the 3-4 November 2015 CYSTINET international conference in Belgrade, Serbia, were surveyed by means of a questionnaire in order to obtain further grey literature and unpublished data. Details of patient data - with due regard to in-country ethical stipulations – as well as information sources and local experts' contacts were also requested from the CYSTINET members. Three of the authors (EH, NFW, PLC) collated the primary source data for a series of 26 cases managed at Hospital of Tropical Diseases in London, United Kingdom, that were subsequently published after the present study was conceived and initiated.[30] Those cases are described here as unpublished, which accurately reflects their status at the time the data for the present study were collated. Ethical approval was obtained where required (Serbia, Portugal, Romania). At all subsequent CYSTINET meetings and conferences, reminders were issued and contributions were also solicited via email. Medical plausibility verifications were conducted (by AA, DS, MK and ASW) on the patient data, which were all anonymized.

Data extraction: All variables for data extraction have been outlined in the research protocol; these were consequently utilized in the data extraction process. Data were extracted by five independent researchers (DS, RM, AA, AF, MK) and in case of uncertainty another expert of the group (ASW) was consulted. Plausibility verifications were carried out on the data extracts saved in Excel sheets, by a different reviewer from the one who had extracted the data.

Definition of variables: Autochthonous cases were defined as not having migrated from or never having travelled to an area outside of Europe that is endemic for *T. solium*. Only if travel/migration history was specifically denied by the patient, was the case considered to be autochthonous; otherwise the information was considered to be not available. Epileptic seizure types were classified as focal onset or generalised onset seizures according to the latest International League against Epilepsy (ILAE) definition.[31] For the evaluation of diagnostic variables computed tomography (CT), magnetic resonance

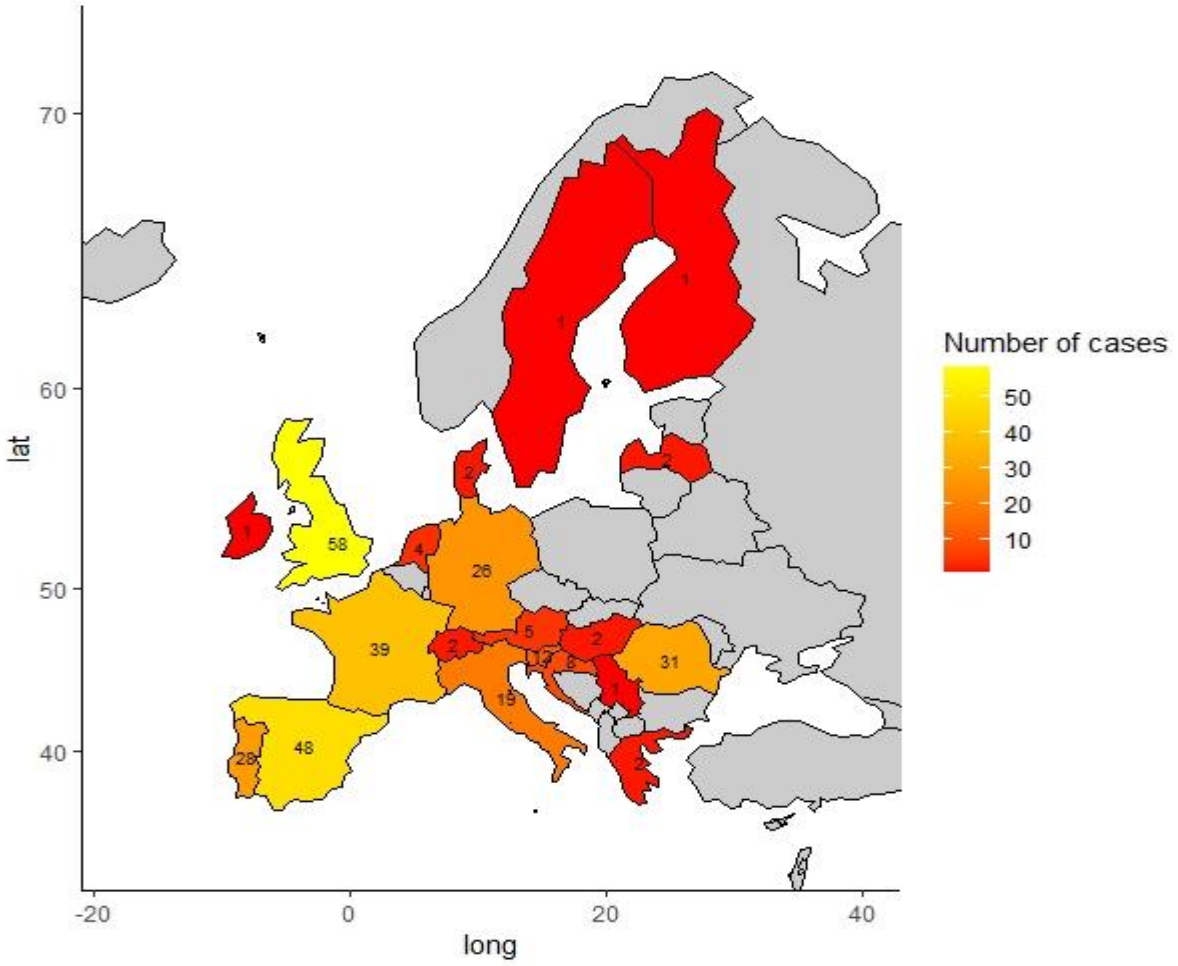
imaging (MRI), soft tissue x-ray, and electroencephalography (EEG) were recorded. Furthermore, variables on location (cerebral: intraparenchymal, intraventricular, subarachnoid; spinal: intra-medullary/extra-medullary, and extra-neural) and stages of the cyst(s) (active: vesicular, colloidal, granular nodular; inactive: calcified) were extracted. In addition, other diagnostic findings such as perilesional edema and hydrocephalus were considered. Of note, neurological signs/symptoms pertaining to intracranial hypertension (ICH) were not recorded as they are heterogenous by nature and were assumed to have been reported inconsistently throughout the included case reports. All information mentioned in the text or visible on pictures was included. Favourable outcomes were defined as "Cured" or "Improved". If patients were free from symptoms and no active cysts were visible on follow-up imaging, the patient was considered as cured. Also, if it was specifically mentioned that the patient was cured. The patient was considered to have improved if at least one active cyst shrank in size or if symptoms after treatment were less intense or less frequent as before.

Statistical analyses: Categorical variables were compared with Chi-square tests and Chi-square tests for trends where applicable. Continuous variables were compared using the Wilcoxon test when non-normally distributed. Statistical analyses were performed using R version 3.6.2.[32]

RESULTS

Search Results

Searching PubMed, EMBASE, Web of Science, Global Health (CABI), and Global Index Medicus identified a total of 13,264 publications. Through Aoister, Open Grey, CYSTINET presentations and through personal communication 52 additional publications were found. After de-duplication, 10,088 remained. After title, abstract and full text screening, 145 publications on individual cases or smaller case series (containing data of overall 211 patients with NCC) were included. The search process is presented in a flowchart in Supplement Figure S1. Through expert consultations we retrieved a further 82 unpublished cases of NCC. Most of the unpublished cases were from the United Kingdom (n=34, 41%) and Romania (n=31, 38%), but we also received case descriptions from Austria, France, Germany and Italy. More than 50% of the published cases were diagnosed and treated in three western European countries, namely Spain (48/211), France (38/211) and Portugal (28/211). A further 16 countries also reported cases, of which four countries reported more than 10 cases (United Kingdom, Germany, Italy and Slovenia; Figure 1, Supplement Table S3).



211 **FIGURE 1.** Map of Europe showing the number of cases included in this analysis
212

213 *Patient demographic and clinical characteristics*

214 *Demographics and migration details*

215 Among the published cases, 53% of those with recorded sex, were female. Median age at diagnosis was
216 32 years (interquartile range 21 to 47); the youngest patient was two years old and the oldest patient
217 was 82 years old. Nearly every fifth (n=38, 19%) patient was a child or an adolescent (aged <18 years;
218 Supplement Figure S2). Most patients (85%) either originated from or travelled to areas highly endemic
219 for *T. solium*. Only 15% of all patients denied having travelled outside Europe; these patients were
220 considered autochthonous cases (Table 1). More than half of those cases either occurred in or had a
221 travel/migration history to/from eastern European countries, e.g. Hungary or Romania. Among the
222 "imported" cases, approximately half of all patients migrated from or had travelled to Latin America,
223 mostly from Ecuador, Colombia, Bolivia or Brazil. Most of these patients were treated in Spain (61%).
224 Most cases from Asia had a travel history from India (22/33); most cases from Africa were diagnosed in

Portugal, the majority originated from Cape Verde (17/44) and Guinea-Bissau (5/44). A substantial proportion of unpublished cases were reported from Romania where most patients had never left Europe or even their country. Hence, almost 50% (32/70) of the unpublished cases were autochthonous cases. Contrary to the published cases, among unpublished cases with travel/migration history, most migrated/travelled from Asia (58%) or Africa (42%).

Neuroimaging and electroencephalography

All patients reported in this paper had neuroimaging performed, but it was not always specified whether this was a CT and/or an MRI. In the majority of cases, diagnostic imaging was performed with a combination of CT and MRI, usually including contrast medium; in only 16% of the cases, diagnosis was based solely on CT scanning. In approximately one quarter ofpatients soft tissue imaging was also performed. Indications for this were most often either extensive findings on neuroimaging or palpable rice corn like cysts/calcifications on clinical examination. Among the published cases, 24 (14%) had an EEG documented (15 with result); of those, 4 had a normal EEG, 3 showed epileptic activity and 8 showed abnormal unspecified patterns. Those were mostly patients with epileptic seizures.

Staging of cysts

Around 90% of all NCC patients (published 89% and unpublished 93%; Table 1) had viable cysts in their brain (most commonly in the parenchyma) or spine. Viable cysts were defined as cysts in vesicular or degenerative stage. The remaining patients presented with calcifications only. There is some indication that children more often had intraparenchymal NCC (26/29, 90%), whereas adults scored higher on intraventricular (39/199, 20%) and subarachnoid NCC (25/197, 13%; Supplement Table S4). Ninety-one (41%) patients had only a single lesion (regardless of whether viable or calcified; Table 1). Of the patients with viable cysts, published and unpublished cases taken together, 108 patients (68%) had at least one cyst with ring enhancement and 85 (59%) had a scolex visible on imaging. Perilesional edema was present in 124 patients (57%; Table 1). There was one case report of a patient who only had one calcification – no viable cysts – but perilesional edema. Fourty-one patients had hydrocephalus, most of which were patients with extraparenchymal or spinal cysts. Five patients with hydrocephalus were described as having only intraparenchymal cysts. Among the published cases, the majority of patients had at least one cyst in the degenerative (colloidal or granular nodular) stage (57%). Twenty-one of the 144 of the patients with available detailed information on the stage of the cysts had calcifications only (Table 1). Five of 27 patients with subarachnoid cysts also had spinal cysts.

Radiological differences by origin of infection

Patients who migrated from Latin America had the highest proportion of extraparenchymal NCC, either only extraparenchymal lesions or in combination with intraparenchymal lesions (47%), and they mostly had multiple lesions (62%). Those migrating from Asia and Africa had the smallest proportion of extraparenchymal (26%) and multiple lesions (42%), respectively. Presentation of European autochthonous cases were in-between the other world regions (Supplement Tables S5/6). Patients with infection contracted in Latin America only seldomly had extraneural lesions (3/50; 6%). This proportion was highest for patients with autochthonous infection in Europe (8/21; 38%).

Neurological signs/symptoms

The most common presentation in both the published (55%) and the unpublished (72%) cases, were epileptic seizures . Children more commonly presented with epileptic seizures than adults (Supplement Table S4). Most of the seizures were of generalised onset. Concomitantly, many patients reported headache episodes (52%). Twenty-three patients presented only with headache (12%) without any other neurological signs/symptoms. More than half of all patients (54%) presented with other neurological signs/symptoms either alone or in combination with headache and/or epileptic seizures (Table 1). Those signs/symptoms were most commonly unsteady gait (27%), cognitive impairment (21%), impaired consciousness (20%) or impaired vision (19%). Also reported were cases with cranial nerve lesions, speech difficulties, meningism and vertigo (Table 2).

Association of neurological signs/symptoms and neuroimaging results

Neurological signs/symptoms varied depending on cyst location, number, stage and other additional findings (Table 3, Figure 2, Supplement Figure S3). Regarding cyst location, presentation with epileptic seizures was more common in patients with intraparenchymal cysts. Epileptic seizures were reported in 66% of patients with intraparenchymal cysts compared with 25% of patients with at least one intraventricular cyst and 36% of patients with at least one subarachnoid cyst. This difference was even more pronounced when excluding patients with cysts at various locations (72% versus 15%/14%, $p<0.005$; Table 3 and Figure 2A). Patients with only intraventricular cysts were more likely to present with headache than patients with only intraparenchymal or subarachnoid cysts (86% versus 43%/57%; $p<0.01$; Table 3). Furthermore, patients with subarachnoid cysts, were significantly older than patients with cysts at other locations (median: 47 years [IQR 32–56 years] versus 31 years [IQR 24–45]; Wilcoxon test $p<0.005$, Supplement Figure S4). The majority of patients who showed hydrocephalus also had headache (67% versus 46%, $p=0.04$) or other neurological signs/symptoms (85% versus 34%, $p<0.005$; Table 3 and Figure 2B).

Regarding cyst stage, patients with cysts in the vesicular stage more commonly presented with headache compared to degenerative and calcified cyst stage (65% versus 44%/38%; p=0.06). Patients with degenerative (71%) or calcified (65%) cyst stage more commonly presented with epileptic seizures (p<0.005; Table 3, Figure 2C). There was no significant difference in the number of patients with other neurological signs/symptoms between the cyst stage (viable/degenerative/calcified: 47%/48%/42%, p=0.84).

With respect to cyst number, patients with single lesions more commonly presented with seizures than patients with multiple lesions (p<0.005; Table 3), but there was no difference for headache or other neurological signs/symptoms. Among the published cases, seven had spinal cysts only. Symptoms ranged from general disorientation and headache, which could indicate undetected cereberal involvement, to brachialgia, brachial paralysis, bladder dysfunction, L5 radiculopathy, steppage gait and cauda equina syndrome. Overall, 30 patients additionally had extra-neural lesions. Most common locations were ocular cysts (n=8), cysts in the thoracic/back muscles (n=10) and calcifications in the thigh muscles (n=7).

Laboratory tests

As determined by the inclusion criteria, all patients had NCC confirmed on neuroimaging. In addition, one hundred and eighty-four patients (63%) had serological testing of which 131 (71%) were positive in any test (serum or CSF, antigen or antibody). Among published cases 73% had a positive test, of the unpublished cases only 68% tested positive (Table 1). For those with information on diagnostic tests available, eight patients were reported to have been tested for antigen (three serum and CSF, four only serum, one only CSF); seven of these patients were antigen positive, one had an indeterminate result. Seventy-one patients were tested for *T. solium* specific antibodies (37 serum and CSF, 34 only serum and 0 only CSF) and 61 (86%) were positive in any test. Western blot was more commonly used than ELISA in both serum and CSF (Supplement Table S7). Patients with single lesions were less commonly positive in any serological test than patients with multiple lesions (46% versus 75%, Supplement Table S8). Also, patients with extraparenchymal lesions more commonly were serologically positive (Supplement Table S8). Thirty patients had stool examined of which none was positive for *T. solium* eggs.

Treatment and outcomes

Anthelminthic therapy was used in the treatment of the majority of NCC cases: 191 patients (81%) were treated with anthelmintics. Most patients received albendazole, either alone (76%) or in combination with praziquantel (15%; Table 1). The duration of anthelmintic treatment ranged from a single dose to three months (praziquantel) and from a single dose to nine months (albendazole). The most common

treatment duration was 10–15 days (Supplement Figure S5), longer for patients with extraparenchymal lesions compared to those with intraparenchymal lesions (Supplement Table S9). Eleven patients with only extraparenchymal lesions were treated with anthelmintic medication, e.g. after extirpation of spinal cysts.

One-hundred-fifty-five patients (73%) received corticosteroid therapy, either dexamethasone or prednisolone/prednisone. Of those, 147 (95%) patients were also treated with anthelmintics, and 8 (5%) patients were treated with steroids alone. Dexamethasone was more frequently used than prednisolone/prednisone (68% versus 41%; some used both; Table 1).

Surgical treatment was performed in 71 patients (40%), mainly patients with intraventricular cysts. Surgical treatment often involved extirpation of the cysts and drainage of the hydrocephalus through ventricular shunting. Twenty-three of 34 (68%) patients with hydrocephalus received ventricular shunting. Extirpated cysts were usually analysed pathologically (Table 1).

The majority of patients presenting with epileptic seizures were put on antiepileptic drugs (AED) unless they had been on AED already. Twenty-five patients (21%) did not receive AED despite presenting with epileptic seizures. The most common AED was carbamazepine (400mg/d), followed by levetiracetam (1000mg/d) and valproic acid (1000mg/d; Supplement Table S10).

When reported, the treatment outcome was favourable in 139/155 (90%) patients, although only 68 (44%) patients were reported to have been cured from NCC. Ten percent of the patients did not have an improvement of symptoms or lesions — some even deteriorated and five patients, of which four were younger than 40 years old, died from the disease during or after treatment (Table 1). Two of the patients who died had intraventricular cysts, one patient concomitantly had a glioblastome multiforme, one patient was living with HIV and developed bronchopneumonia during therapy, and the fifth patient died from epileptic seizures. Supplement Table S11 shows treatment outcome by various parameters. The outcome did not differ significantly for any of the parameters ($p>0.05$ for all). Children more commonly were cured through therapy than adults (20/35 [57%] versus 48/120 [40%]).

TABLE 1. Characteristics of published and unpublished NCC cases

		Published cases (n=211)	**Unpublished cases (n=82)**	**Total (n=293)**
		n (%)[1]	n (%)[1]	n (%)[1]
Sex	Female	102/191 (53)	47/78 (60)	149/269 (55)
	Male	89/191 (47)	31/78 (40)	120/269 (45)

Age at diagnosis	Median age in years [IQR]	32 [21–47]	35 [26–46]	33 [23–47]
	Children (<18 years)	38/198 (19)	4/79 (5)	42/277 (15)
	Adults	160/198 (81)	75/79 (95)	235/277 (85)
Autochthonous cases		26/174 (15)	32/70 (46)	58/244 (24)
Travel/Migration[2]		148/174 (85)	38/70 (54)	186/244 (76)
	Africa	43/148 (29)	16/38 (42)	59/186 (32)
	Asia	33/148 (22)	22/38 (58)	55/186 (30)
	Caribbean	11/148 (7)	1/38 (3)	12/186 (6)
	Latin America	61/148 (41)	9/38 (24)	70/186 (38)
	Middle East	3/148 (2)	0/38 (0)	3/186 (2)
Signs/ Symptoms	Epileptic seizures	109/199 (55)	49/68 (72)	158/266 (59)
	Focal onset seizures	20/73 (27)	2/33 (6)	22/106 (21)
	Generalised onset seizures	53/73 (73)	31/33 (94)	84/106 (79)
	Headache	92/187 (49)	40/68 (59)	132/255 (52)
	Other neurological signs/symptoms	90/198 (46)	34/35 (97)	125/233 (54)
Serology (Serum/CSF)	Antigen or antibody positive	89/122 (73)	42/62 (68)	131/184 (71)
	Antibody positive	63/75 (84)	NA	63/75 (84)
	Antigen positive	7/9 (78)	NA	7/9 (78)
Neuroimaging /EEG	CT	151/192 (79)	36/39 (92)	187/231 (81)
	CT with contrast	58/78 (74)	NA	58/78 (74)
	Only CT	28/151 (19)	2/36 (6)	30/187 (16)
	MRI	165/194 (85)	39/41 (95)	204/235 (87)
	MRI with contrast	127/132 (96)	NA	127/132 (96)
	Only MRI	40/165 (24)	3/32 (9)	43/197 (22)
	Soft tissue x-ray	39/177 (22)	NA	39/116 (22)
	EEG	24/167 (14)	NA	24/125 (14)
Results on neuroimaging	Single lesion	65/179 (36)	26/43 (60)	91/222 (41)
	Multiple lesions	114/179 (63)	17/43 (40)	131/222 (59)
	Viable cysts	177/198 (89)	57/61 (93)	234/259 (90)
	Single	75/167 (45)	28/41 (68)	103/208 (50)
	Multiple	92/167 (55)	13/41 (32)	105/208 (50)
	Enhancing cysts	99/145 (68)	9/13 (69)	108/158 (68)
	Cysts with scolex	80/134 (60)	5/9 (56)	85/143 (59)
	Calcifications	69/182 (38)	9/12 (75)	78/194 (40)
	Single	6/60 (10)	NA	6/60 (10)
	Multiple	54/60 (90)	NA	54/60 (90)
	Perilesional edema	83/156 (53)	41/62 (66)	124/218 (57)
	Hydrocephalus	41/185 (22)	NA	41/185 (22)
	Vesicular stage[3]	41/144 (29)	NA[5]	41/144 (29)

	Colloidal/granular nodular stage[3]	82/144 (57)	NA[5]	82/144 (57)
	Calcified stage[3]	21/144 (15)[4]	NA[5]	21/144 (15)[4]
Cyst(s)/Calcification(s) location[2]	Cerebral	175/185 (95)	56/56 (100)	231/241 (96)
	Intraparenchymal	149/175 (85)	52/56 (93)	201/231 (87)
	Intraventricular	40/175 (23)	4/56 (7)	44/231 (19)
	Subarachnoid	23/175 (13)	3/56 (5)	26/231 (11)
	Spinal	16/168 (11)	2/3 (67)	18/171 (12)
	Intra-medullary	3/16 (19)	1/1 (100)	4/17 (24)
	Extra-medullary	13/16 (81)	0/1 (0)	13/17 (76)
	Extra-neural	23/138 (17)	7/12 (58)	30/150 (20)
Treatment	Surgery	64/162 (40)	7/14 (50)	71/176 (40)
	Pathological examination	49/56 (88)	5/6 (83)	54/62 (87)
	Anthelmintic therapy	136/175 (78)	55/62 (89)	191/237 (81)
	Praziquantel and Albendazole	19/136 (14)	9/55 (16)	28/191 (15)
	Praziquantel only	14/136 (10)	3/55 (5)	17/191 (9)
	Albendazole only	103/136 (76)	43/55 (78)	146/191 (76)
	Corticosteroids	111/166 (67)	44/47 (94)	155/213 (73)
	Prednisolone/Prednisone	30/78 (38)	9/17 (53)	39/95 (41)
	Dexamethasone	48/78 (62)	17/17 (100)	65/95 (68)
	Anti-epileptic treatment[2]	76/162 (47)	32/35 (91)	108/197 (55)
	Carbamazepine/Oxcarbazepine	13/42 (31)[2]	NA	13/42 (31)[2]
	Phenobarbitone	3/42 (7)[2]	NA	3/42 (7)[2]
	Phenytoin	6/42 (14)[2]	NA	6/42 (14)[2]
	Valproic acid	8/42 (19)[2]	NA	8/42 (19)[2]
	Lamotrigine	3/42 (7)[2]	NA	3/42 (7)[2]
	Levetiracetam	11/42 (26)[2]	NA	11/42 (26)[2]
	Clobazam	1/42 (2)[2]	NA	1/42 (2)[2]
Outcome	Cured	68/155 (44)	NA	68/155 (44)
	Improved	71/155 (46)	NA	71/155 (46)
	No change, deteriorated	11/155 (7)	NA	11/155 (7)
	Death	5/155 (3)	NA	5/155 (3)

1 Counted, if explicitly stated, visible on imaging or if it could be inferred; the denominator varies between variables.

2 More than one answer possible; hence the sum of the percentages can exceed 100%.

3 Stage of the cyst: Degenerative if at least one cyst is in the degenerative stage; vesicular and calcified stage if all cysts are in the respective stage. Hence, the numbers of viable cysts/calcifications do not match the results by stage.

4 This is the proportion of patients with only calcified stage among those with detailed information of the stage of the cysts. The overall proportion of patients with only calcified cysts is 10%.

5 Due to limited information, no analyses were conducted for unpublished cases.

IQR Interquartile range

NA Not available

363

364 **TABLE 2.** Other neurological signs/symptoms

Neurological sign/symptom	Cases with neurological signs/symptoms (N=125)[2]
Unsteadiness of gait[1]	33 (33%)
Cognitive impairment	26 (21%)
Impaired consciousness	25 (20%)
Impaired vision[1]	24 (19%)
Limb paresis	21 (17%)
Speech difficulties[1]	14 (11%)
Cranial nerves lesions	14 (11%)
Limb Ataxia	9 (7%)
Meningism[3]	9 (7%)
Impaired sensation[1]	9 (7%)
Vertigo	8 (6%)
Limb spasticity	6 (5%)
Bladder dysfunction	4 (3%)

365

366 1 Speech difficulties, unsteadiness of gait, impaired vision and impaired sensation were not specified in more detail in the case descriptions, therefore origin (peripheral/central,
367 cerebral/cerebellar etc.) remains unclear.
368 2 Most symptomatic cases reported more than one neurological sign/symptom, therefore column totals are larger than N=125 or 100%, respectively.
369 3 Signs/symptoms described as: "meningeal signs, neck stiffness, meningism, neck rigidity"

TABLE 3. Neurological signs/symptoms stratified by cyst(s) location, number, radiological characteristics and stage[1]

			Epileptic seizures		**Headache**		**Other neurological signs/symptoms[5]**	
			n (%)	p	n (%)	p	n (%)	p
Cyst(s) location	Intraparenchymal cyst(s)	Yes	129/196 (66)	p<0.001	96/183 (52)	p=0.31	95/166 (57)	P=0.16
		No	5/36 (14)		24/38 (63)		30/39 (77)	
	Intraventricular cyst(s)	Yes	10/40 (25)	p<0.001	32/44 (73)	p=0.008	29/41 (71)	p=0.14
		No	121/188 (64)		84/173 (49)		80/161 (50)	
	Subarachnoid cyst(s)	Yes	9/25 (36)	p=0.05	18/24 (75)	p=0.04	17/24 (71)	p=0.57
		No	119/201 (61)		96/191 (50)		91/177 (51)	
	Only intraparenchymal[2]		73/102 (72)	p<0.001	39/91 (43)	p=0.01	30/101 (30)	p<0.001
	Only intraventricular[2]		2/13 (15)		12/14 (86)		10/14 (71)	
	Only subarachnoid[2]		1/7 (14)		4/7 (57)		5/7 (71)	
Cyst number	Single		64/89 (72)	p<0.001	35/81 (43)	p=0.14	34/71 (53)	p=0.60
	Multiple		62/126 (49)		68/124 (55)		63/119 (48)	
Concomitant findings	Ring enhancement[3]	Yes	67/106 (63)	p=0.06	41/94 (44)	p=0.08	44/100 (44)	p=0.78
		No	21/48 (44)		30/48 (62)		25/50 (50)	
	Perilesional edema[3]	Yes	87/121 (72)	p<0.001	50/113 (44)	P=0.009	48/99 (48)	p=0.60
		No	41/91 (45)		57/89 (64)		55/88 (62)	
	Hydrocephalus	Yes	7/36 (19)	p<0.001	26/39 (67)	p=0.04	34/40 (85)	p<0.001
		No	90/140 (64)		59/128 (46)		52/139 (34)	
Stage	Vesicular stage		11/32 (34)	p<0.005	22/34 (65)	p=0.06	16/34 (47)	p=0.84
	Degenerative stage[4]		82/116 (71)		47/107 (44)		46/95 (48)	
	Calcified stage		15/23 (65)		9/24 (38)		10/24 (42)	

1 Only patients with detailed information on stage of the cyst(s) were included (published and unpublished cases). Data refer to the known information on epileptic seizures, headache and other neurological signs/symptoms by group categorised in the left hand column (e.g. intraparenchymal cysts). "n" gives the number of patients with the respective sign/symptom. For example: of the 196 patients with intraparenchymal cysts, 129 (66%) presented with epileptic seizures. Apart from the category "stage", more than one criterion was possible per category.

2 Patients with cysts at various locations (intraparenchymal, intraventricular, subarachnoid) were excluded.

3 Ring enhancement/perilesional edema around at least one lesion

4 Degenerative stage: colloidal or granular nodular stage

5 Detailed list of other neurological findings can be found in Table 2

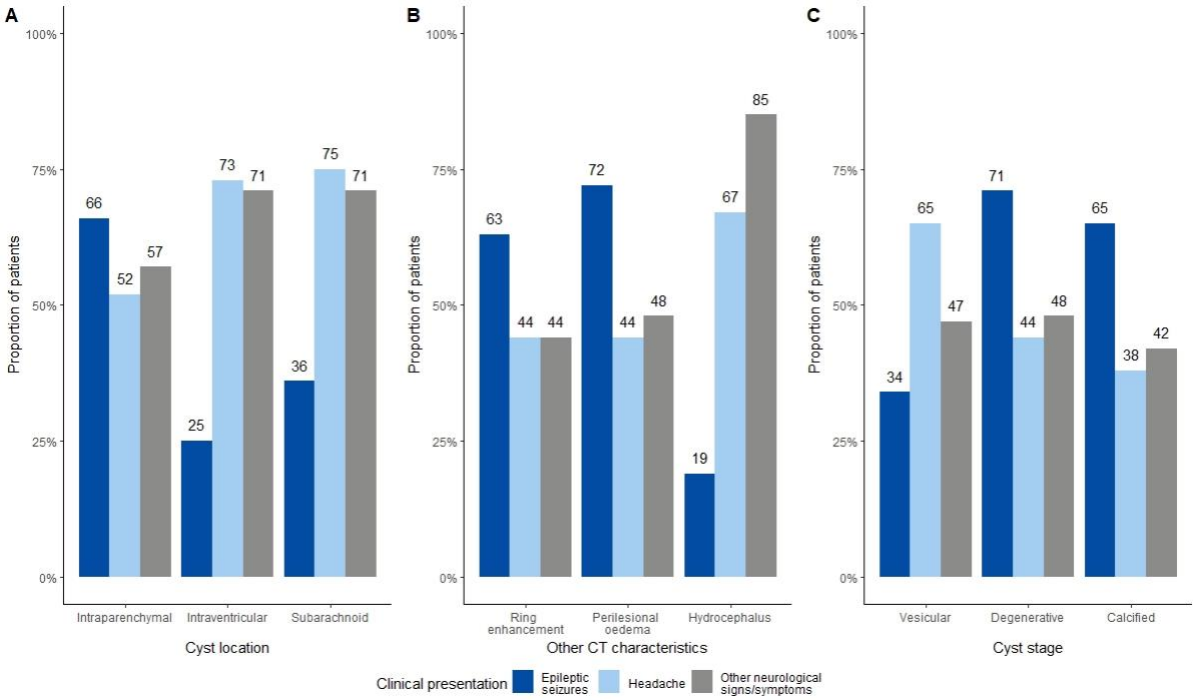


FIGURE 2. Clinical presentation by cyst location (A), neuroimaging findings (B) and cyst stage (C). For cyst location and CT characteristics more than one criterion was possible. * Stage of the cyst: Degenerative if at least one cyst is in the degenerative stage; vesicular and calcified stage if all cysts are in the respective stage.

Discussion

In this study, we present demographic and clinical details of almost 300 patients with NCC in the European context, based on a systematic literature search, including grey literature, in addition to unpublished NCC cases collected from colleagues through the European network CYSTINET. We report several novel observations as well as observations that are in line with previously published literature.[16–19,33,34]

Origins of infection

We were able to show that most patients treated for NCC in Europe are migrants from countries endemic for *T. solium*. However, confirming the exact region of origin of infection is a challenge, as NCC often becomes symptomatic only several years after first exposure. There seems to be only few regions in Europe where the full lifecycle of *T. solium* is still present and in those regions, autochthonous NCC cases can still occur.[18] Our search yielded relatively more autochthonous cases among unpublished NCC cases compared with published cases. This is likely due to reporting differences between countries of published and unpublished cases, e.g. especially the reported cases in Romania were mostly unpublished. The number of autochthonous cases reported should be interpreted with caution, as

routine travel history reported usually included only a few non-standardized questions and did not include a detailed epidemiologic interview. Also, it only requires one tapeworm carrier to infect other people with cysticercosis – for autochthonous cases, this person could either be another local person but could also be a migrant which makes it difficult to trace back the source of infection. In our review, we also found a considerably lower proportion of autochthonous cases compared with a review on cysticercosis in Europe, by Zammarchi et al. in 2013, which found 62% of cysticercosis cases being autochtonous cases which may suggest improvements in the disruption of the *T. solium* lifecycle. [16]

Clinical characteristics and related findings on neuroimaging

The sites and stages of cysts influences how patients with NCC present. With regards to site, most symptomatic patients with intraparenchymal cysts presented with epileptic seizures compared to patients with extraparenchymal cysts who were more likely to present with non-specific symptoms like headache. Patients with extraparenchymal cysts were significantly older at diagnosis. This may be because patients infected at an older age were more likely to develop extraparenchymal NCC e.g. due to comorbidities and immunological factors or because symptoms were less specific and therefore diagnosis was made at a later stage.[35] These findings, i.e. patients with extraparenchymal lesions being older and showing more non-specific signs/symptoms, concur with NCC data published from Mexico.[5] The number of patients with autochthonous cases was rather low so it was difficult to draw conclusions on disease presentation in comparison to patients you were infected in Latin America, Asia or Africa.
Ring enhancing lesions and those with perilesional edema also seemed to predispose to presentation with epileptic seizures. However, although epileptic seizures occurred frequently under those conditions, around half of the cases were also accompanied by other neurological signs and symptoms, including headache. The latter, however, was frequently reported in extraparenchymal NCC (intraventricular and subarachnoid NCC) and when hydrocephalus was present. Looking at cyst stage, headache prevailed in the vesicular stage, where little to no inflammation was evident on radiology, the pathophysiology of headache under these conditions is not clear (ASW unpublished data), whereas epileptic seizures were the predominant neurological symptom during the degenerative stage of the cyst(s)
It is well established that clinical manifestations of NCC can vary from completely asymptomatic infection (54% of NCC patients in a study of Monteiro de Almeida et al.[36]) to severe disease and death.[2,37] The major determinants of the characteristics of symptomatic NCC are the number of cysts, their location, their stage and the degree of inflammation.[35,38] It has been shown previously that NCC can mimic almost any neurological disorder[39], but to date neurological signs/symptoms other than epileptic seizures or headache are thought to occur in the minority of patients.[1] In concordance with previous

studies, we found a high proportion of epileptic seizures among NCC patients.[1,16,40] However, in our study of European presentations, we found that more than half of all NCC patients presented with other neurological signs/symptoms. This may reflect some publication bias, as unusual case presentations more likely come to the attention of a clinician and be published than patients presenting with well-known signs/symptoms of NCC. Also, patients presenting in low-income and middle-income countries may be more likely to present later to health services than in high-income countries, often with more severe symptoms and subtle neurological signs and symptoms may not be identified or recorded as consistently.

Regarding publications included in our study, the classification of neurological signs/symptoms other than epileptic seizures and headache was challenging as description of signs/symptoms could be vague and their origin remaining uncertain (see Table 3). Remarkably, in our study, impaired cognitive function appeared to be one of the most frequent other neurological signs. In the included publications, EEG was rarely performed and predominantly only when epileptic seizures were present. Therefore, non-convulsive seizures that could account for impaired cognitive function may not have been identified. A high proportion of cognitive decline (87.5%), dementia (12.5%) or altered mental state (28%) in NCC patients has also been observed in previous studies.[1,41,42]

Special considerations

According to previously published studies, between 1.5% and 3% of NCC patients are estimated to have spinal cysts.[43–48] The true proportion is likely higher than 3% as spinal imaging is not routinely performed. In our dataset, this proportion was higher (18/171; 10.5%). For example, a study in Peru found spinal cysts in 17 of 28 (61%) patients with basal subarachnoid cysts, supporting a recommendation to perform spinal imaging in all patients with basal subarachnoid NCC.[49] In our dataset, 5/27 (19%) patients with subarachnoid NCC also had spinal cysts, while not all 27 patients had cysts in the basal subarachnoid space. Combined cerebral and spinal imaging was not often done, or at least not often reported in our European cases and may result in an underestimation of the true burden of spinal NCC in the context of subarachnoid NCC in our study population.

In addition to spinal NCC, we would like to highlight the identification of perilesional edema around a calcification. In our study population, we found one patient where perilesional edema around a calcification was present. Until recently, calcifications were considered inactive in terms of immune response. However, it seems that calcified cysticerci can temporarily release residual antigen that may trigger an immune response.[50–52] Why this happens is still not entirely clear. It could make treatment in patients with concomitant viable cysts and calcifications challenging, as epileptic seizures may still occur after cyst resolution (after anthelmintic therapy or spontaneously) and therefore discontinuation

of AED after resolution of viable cysts in patients with concomitant intermittent perilesional edema around calcifications may carry risks. Clinicians should be aware that this may occur. Perilesional edema around calcifications should not be treated with anthelmintic drugs and corticosteroid therapy is not routinely recommended.[53]

The value of serology and neuroimaging

In our study, serological testing of any kind for *T. solium* in CSF and/or serum was reported in only 61% of cases. It is likely that serological testing was performed as confirmation after neuroimaging, however, from our dataset we could not establish why serological testing was performed in some cases and not others, nor the time point when it was performed in relation to presentation. Serological detection of *T. solium* antigen and antibodies is not yet widely available throughout Europe. There are only a few commercial tests available on the market, and these are often supplied in a form that is not always suitable for laboratories that see only occasional cases. In addition, in-house assays are not easy to implement and validate for laboratories due to a lack of well-defined reference sera. A commercial antigen test has only been available in the last few years. Until then, in-house assays relied on monoclonal antibodies which were not readily available. The low number of antigen tests reported is particularly striking, as there is good evidence that antigen follow-up is useful in the context of therapeutic outcome monitoring in symptomatic active NCC cases. Here, clear and easily available guidelines for *T. solium* serological testing seem desirable. Although antigen testing was performed much less frequently than antibody testing, it showed higher sensitivity. However, it must be taken into account that the proportion of patients with active stage lesions was rather high which may have influenced the sensitivity of the antigen ELISA. Still, one-third of the confirmed NCC cases, more so those with single lesions, were not positive in any serological assay which demonstrates the need for establishing a standardized approach to immunodiagnostic testing in European laboratories.

Regarding neuroimaging, a combination of MRI and CT imaging is recommended in the Clinical Practice Guidelines for the Diagnosis and Treatment of NCC by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH) guidelines and in the WHO guidelines on management of *Taenia solium* neurocysticercosis, because MRI has a higher sensitivity for detecting active NCC lesions and CT imaging has a higher sensitivity for detecting calcifications.[53,54] In our study, a third of all patients only had one type of neuroimaging performed, which may have lead to an underreporting of both active and inactive NCC lesions.

Treatment of symptomatic patients with neurocysticercosis

In the IDSA/ASTMH guidelines, different recommendations for anthelmintic treatment are given for different manifestations of NCC.[53] Surgical removal and/or ventricular shunting in the case of increased intracranial pressure is recommended for patients with intraventricular cysts. For patients with NCC-related hydrocephalus or diffuse cerebral edema, corticosteroid therapy without anthelmintics is recommended. For patients with one or two intraparenchymal cysts, 15mg/kg/day albendazole is advised for 10-14 days with treatment extendended if no effect in terms of cyst resolution is shown; for patients with more than two viable intraparenchymal cysts it is recommended to combine albendazole with praziquantel 50mg/kg/day is recommended.[53] Generally, treatment recommendations do not differ for children and adults, apart from an adjustment of anthelmintic drug dosage. In our dataset, which includes many cases that were diagnosed and treated before the above guidelines were published in 2018, approaches to treatment were extremely varied and longer durations and higher dosages were given to patients with more severe manifestations or to non-responders. This reflects the importance of having clear consensus guidance for treatment in order to improve safety and efficacy, and to better understand treatment outcomes.

In our European population, corticosteroids were mostly administered for the same duration as anthelmintic therapy although surprisingly, many patients received corticosteroids for shorter time than anthelmintics. This had been recommended previously[7,8], but is nowadays not recommended. However, this could also be due to the fact that concurrent steroid therapy was not consistently reported. For corticosteroid therapy, the IDSA/ASTMH guidelines recommend steroids for the entire duration of the anthelmintic therapy and even starting 3 to 4 days in advance. Generally, dexamethasone and prednisolone are recommended. For dexamethasone, a dosage of 0.1mg/kg/d is used for patients with intraparenchymal cysts and up to 0.2mg/kg/day for patients with extraparenchymal cysts in the basal cisterns or Sylvian fissure. Successful treatment is contingent on finding the right steroid dose which on the one hand prevents side effects of anthelmintic therapy (i.e. epileptic seizures, severe headache or increased intracranial pressure), but on the other hand also does not suppress the effect of anthelmintic drugs. This is particularly important when treating with a combination therapy of albendazole and praziquantel, as there are enzymatic interactions with dexamethasone, which may lower plasma levels of praziquantel.[55] The IDSA/ASTMH guidelines do not specify whether steroids should be given even after anthelmintic therapy has ended, but do recommendthat steroids should be tapered if they have been given for more than two weeks.[53] It is important to note that the cysticidal effects of anthelmintic therapy may last beyond the end of the treatment cycle, especially with combination therapy with albendazole and praziquantel, and reducing steroid doses over a longer period may be advisable in these cases, at least until disappearance of any perilesional oedema.

We found different AEDs used in patients treated in our European population. Whilst AEDs are recommended for all patients with epileptic seizures according to IDSA/ASTMH guidelines, no recommendation on the type is given; choice should be based on local availability, cost, drug-drug interactions, and potential side effects.[53]

Recommendations for diagnosis and treatment of neurocysticercosis

With this publication we would like to raise the awareness of NCC among clinicians working in European countries. While a travel history to or from endemic countries may support a suspected diagnosis of NCC, the absence of a relevant travel history does not exclude the presence of NCC. In addition, NCC remains predominantly a neuroradiological diagnosis, which means that performing a neuroradiological examination, preferably CT and MRI combined, should be the first priority. At present, serological testing plays only a supportive role in the case of suspicious cerebral lesions on imaging. In addition, the possibility of spinal NCC and temporary perilesional edema around calcifications must be considered and neuroimaging tailored to answer these questions.

With a few exceptions, mainly regarding the availability of serological tests and some drugs, until guidelines tailored to the European context may become available, the IDSA/ASTMH guidelines can, for the time being, be applied to the European context, although there may be only limited access to MRI in some areas of Europe. Based on our experience with the IDSA/ASTMH guidelines, we recommend that he next update reconsiders the treatment guidelines for (co-existing) hydrocephalus and the length and dose of concomitant steroid therapy in combination therapy with albendazole and praziquantel.

Neurocysticercosis in the context of migration and travel medicine

We were able to demonstrate that NCC occurs in Europe albeit most of the cases occurred among migrants and travellers. With increasing travel and migration, an increase in NCC cases in Europe can also be expected, although globally the number of NCC cases is decreasing.[56] This phenomenon has been described for other neglected tropical diseases before.[57] Migrants often face inequities in access to healthcare which hampers diagnosis of infectious diseases, and which may have been even more pronounced during the COVID-19 pandemic.[58,59] There has been increasing effort by the International Society on Travel Medicine to promote migrant health and to bring to attention diseases that more commonly occur among migrants. Hence, this study can also serve this purpose.

Strengths and limitations

The strength of the current paper lies in the combination of original patient data from unpublished NCC cases combined with patient characteristics gathered through an exhaustive systematic literature search including grey literature, in several major European languages. Detailed clinical and demographic characteristics of NCC patients diagnosed and treated in Europe have not previously been so comprehensively summarized in one document, and this study will therefore be of value to any clinician in Europe engaged in the diagnosis or treatment of NCC. Europe is a unique setting for NCC as *T. solium* is not highly prevalent while diagnostic facilities, particularly neuroimaging, are widely available. Regardless, a number of important limitations should be acknowledged. Full text access to the huge number of identified NCC related publications worldwide was not possible, and neither was it possible to acquire access to all country-specific publications. Inherent publication biases are, however, likely to be of greater importance: a) only selected cases being published, and b) often no detailed clinical information being provided in case reports. Also, sharing of unpublished cases, as well as grey literature, depends on research interests and cooperation, and identifyingall unpublished NCC cases in Europe exceeded our research capacity. Thus, the data presented in this study are prone to bias, potentially towards more over-representation of more unusual cases. In addition, assessment of outcomes is limited by lack of standardisation of timing at which the outcome may have been determined.

Conclusions

The synthesis of knowledge of and information about NCC in the European context contained in this publication is unprecedented. NCC represents a rare disease for European clinicians and hence clinical familiarity outside specialist centres is most likely scarce. The current publication contributes to a better understanding of the origin of infection with *T. solium*, clinical characteristics, diagnosis and treatment of patients suffering from NCC in Europe. These data highlight that NCC causes considerable morbidity in patients diagnosed in Europe and that overall treatment outcomes can be improved. In some patients, NCC is a cause of death. Due to the complexity of the life cycle of *T. solium* and the latency until signs and/or symptoms appear, reliable multi-/interdisciplinary data are needed to establish standardized context-specific evidence-based management guidelines for practising clinicians in Europe and beyond.

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Data Availability Statement: In this study, we report data from mostly published cases. The references to these cases are given in the supplementary material and the extracted data were published under the following doi: 10.14459/2021mp1638110

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