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► To cite this version:

Dominik Stelzle, Annette Abraham, Miriam Kaminski, Veronika Schmidt, Robert de Meijere, et al.. Clinical characteristics and management of neurocysticercosis patients: a retrospective assessment of case reports from Europe. *Journal of Travel Medicine*, 2023, 30 (1), pp.taac102. 10.1093/jtm/taac102 . pasteur-04664793

HAL Id: pasteur-04664793

<https://pasteur.hal.science/pasteur-04664793v1>

Submitted on 31 Jul 2024

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1 Article

2 Clinical characteristics and management of 3 neurocysticercosis patients: a retrospective assessment 4 of case reports from Europe

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53 **Abstract:**

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

59 **Methods:** We conducted a systematic search of published and unpublished data on patients diagnosed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

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

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

69

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

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75 **INTRODUCTION**

76 Neurocysticercosis (NCC) is caused by the tapeworm *Taenia solium*, a zoonotic parasite which has a pig-
77 human-environment life cycle. Humans get NCC by ingesting parasite eggs, which are shed through
78 feces of *T. solium* tapeworm carriers. Through environmental contamination and lack of hygiene these
79 eggs can accidentally be ingested by humans. Once in the intestines, the larvae, which are released from
80 eggs, cross the intestinal mucosa into the circulatory system through which they are transported to
81 multiple organs, where they encyst (cysticerci). When these cysticerci affect the central nervous system
82 (CNS), the disease is called NCC. Cysts can persist in the CNS for several years without causing any
83 neurological signs/symptoms. Signs and symptoms are pleomorphic¹⁻⁴, often resulting from
84 degeneration of the cysts and associated inflammatory host immune reaction. The most common
85 neurological signs/symptoms are epileptic seizures, headache episodes, focal neurological deficits and
86 signs of raised intracranial pressure.¹

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

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

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

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

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

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

114 **METHODS**

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

124 **Search methods:** PubMed, EMBASE, Web of Science, Global Health (CABI), Global Index Medicus
125 coupled with Aoister and Open Grey were searched for articles published between January 2000 to May
126 2019. Supplement Table S1 contains the precise search terms and dates. Moreover, each CYSTINET
127 researcher searched for grey literature in their native countries (25 countries; the list of countries can be
128 found under this link: <http://www.cystinet.org/the-action/participating-countries/>); references of
129 included literature were evaluated for relevance and included if they met the inclusion criteria. No
130 language restriction was applied; only studies on humans were included. (Systematic) reviews were
131 screened for additional references.^{16,17,19}

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

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

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

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

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

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

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

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

189 **Statistical analyses:** Categorical variables were compared with Chi-square tests and Chi-square tests
190 for trends where applicable. Continuous variables were compared using the Wilcoxon test when non-
191 normally distributed. Statistical analyses were performed using R version 3.6.2.³²

192

193 **RESULTS**

194 *Search Results*

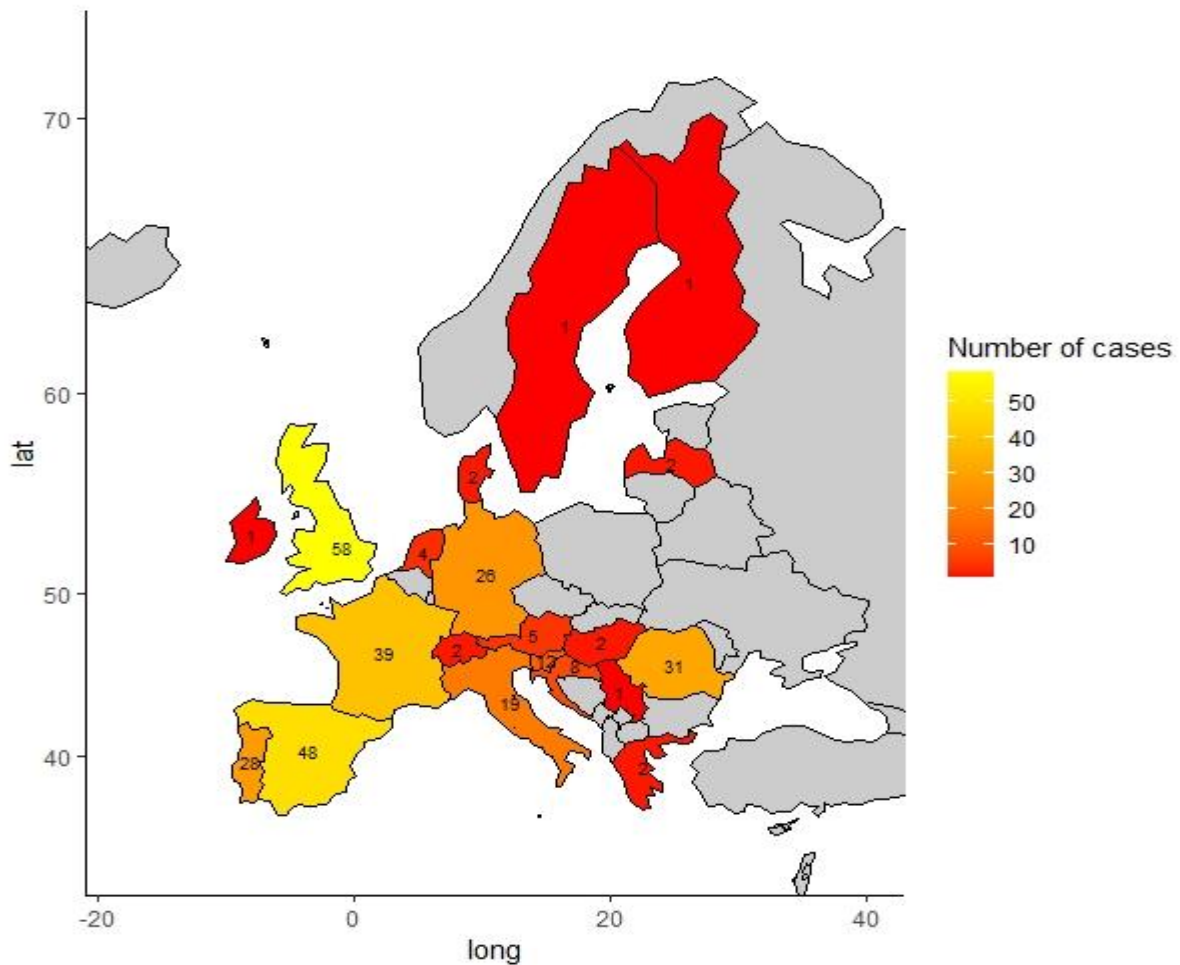
195 Searching PubMed, EMBASE, Web of Science, Global Health (CABI), and Global Index Medicus
196 identified a total of 13,264 publications. Through Aoister, Open Grey, CYSTINET presentations and
197 through personal communication 52 additional publications were found. After de-duplication, 10,088
198 remained. After title, abstract and full text screening, 145 publications on individual cases or smaller
199 case series (containing data of overall 211 patients with NCC) were included. The search process is
200 presented in a flowchart in Supplement Figure S1. Through expert consultations we retrieved a further
201 82 unpublished cases of NCC. Most of the unpublished cases were from the United Kingdom (n=34,
202 41%) and Romania (n=31, 38%), but we also received case descriptions from Austria, France, Germany
203 and Italy. More than 50% of the published cases were diagnosed and treated in three western European
204 countries, namely Spain (48/211), France (38/211) and Portugal (28/211). A further 16 countries also
205 reported cases, of which four countries reported more than 10 cases (United Kingdom, Germany, Italy
206 and Slovenia; Figure 1, Supplement Table S3).

207

208

209

210



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

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

230

231 *Neuroimaging and electroencephalography*

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

240

241 *Staging of cysts*

242 Around 90% of all NCC patients (published 89% and unpublished 93%; Table 1) had viable cysts in their
243 brain (most commonly in the parenchyma) or spine. Viable cysts were defined as cysts in vesicular or
244 degenerative stage. The remaining patients presented with calcifications only. There is some indication
245 that children more often had intraparenchymal NCC (26/29, 90%), whereas adults scored higher on
246 intraventricular (39/199, 20%) and subarachnoid NCC (25/197, 13%; Supplement Table S4). Ninety-one
247 (41%) patients had only a single lesion (regardless of whether viable or calcified; Table 1). Of the patients
248 with viable cysts, published and unpublished cases taken together, 108 patients (68%) had at least one
249 cyst with ring enhancement and 85 (59%) had a scolex visible on imaging. Perilesional edema was
250 present in 124 patients (57%; Table 1). There was one case report of a patient who only had one
251 calcification – no viable cysts – but perilesional edema. Forty-one patients had hydrocephalus, most of
252 which were patients with extraparenchymal or spinal cysts. Five patients with hydrocephalus were
253 described as having only intraparenchymal cysts. Among the published cases, the majority of patients
254 had at least one cyst in the degenerative (colloidal or granular nodular) stage (57%). Twenty-one of the
255 144 of the patients with available detailed information on the stage of the cysts had calcifications only
256 (Table 1). Five of 27 patients with subarachnoid cysts also had spinal cysts.

257

258 *Radiological differences by origin of infection*

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

266

267 *Neurological signs/symptoms*

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

277

278 *Association of neurological signs/symptoms and neuroimaging results*

279 Neurological signs/symptoms varied depending on cyst location, number, stage and other additional
280 findings (Table 3, Figure 2, Supplement Figure S3). Regarding cyst location, presentation with epileptic
281 seizures was more common in patients with intraparenchymal cysts. Epileptic seizures were reported
282 in 66% of patients with intraparenchymal cysts compared with 25% of patients with at least one
283 intraventricular cyst and 36% of patients with at least one subarachnoid cyst. This difference was even
284 more pronounced when excluding patients with cysts at various locations (72% versus 15%/14%,
285 $p<0.005$; Table 3 and Figure 2A). Patients with only intraventricular cysts were more likely to present
286 with headache than patients with only intraparenchymal or subarachnoid cysts (86% versus 43%/57%;
287 $p<0.01$; Table 3). Furthermore, patients with subarachnoid cysts, were significantly older than patients
288 with cysts at other locations (median: 47 years [IQR 32–56 years] versus 31 years [IQR 24–45]; Wilcoxon
289 test $p<0.005$, Supplement Figure S4). The majority of patients who showed hydrocephalus also had
290 headache (67% versus 46%, $p=0.04$) or other neurological signs/symptoms (85% versus 34%, $p<0.005$;
291 Table 3 and Figure 2B).

292 Regarding cyst stage, patients with cysts in the vesicular stage more commonly presented with
293 headache compared to degenerative and calcified cyst stage (65% versus 44%/38%; $p=0.06$). Patients
294 with degenerative (71%) or calcified (65%) cyst stage more commonly presented with epileptic seizures
295 ($p<0.005$; Table 3, Figure 2C). There was no significant difference in the number of patients with other
296 neurological signs/symptoms between the cyst stage (viable/degenerative/calcified: 47%/48%/42%,
297 $p=0.84$).

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

306

307 *Laboratory tests*

308 As determined by the inclusion criteria, all patients had NCC confirmed on neuroimaging. In addition,
309 one hundred and eighty-four patients (63%) had serological testing of which 131 (71%) were positive in
310 any test (serum or CSF, antigen or antibody). Among published cases 73% had a positive test, of the
311 unpublished cases only 68% tested positive (Table 1). For those with information on diagnostic tests
312 available, eight patients were reported to have been tested for antigen (three serum and CSF, four only
313 serum, one only CSF); seven of these patients were antigen positive, one had an indeterminate result.
314 Seventy-one patients were tested for *T. solium* specific antibodies (37 serum and CSF, 34 only serum and
315 0 only CSF) and 61 (86%) were positive in any test. Western blot was more commonly used than ELISA
316 in both serum and CSF (Supplement Table S7). Patients with single lesions were less commonly positive
317 in any serological test than patients with multiple lesions (46% versus 75%, Supplement Table S8). Also,
318 patients with extraparenchymal lesions more commonly were serologically positive (Supplement Table
319 S8). Thirty patients had stool examined of which none was positive for *T. solium* eggs.

320

321 *Treatment and outcomes*

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

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

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

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

338 The majority of patients presenting with epileptic seizures were put on antiepileptic drugs (AED) unless
 339 they had been on AED already. Twenty-five patients (21%) did not receive AED despite presenting with
 340 epileptic seizures. The most common AED was carbamazepine (400mg/d), followed by levetiracetam
 341 (1000mg/d) and valproic acid (1000mg/d; Supplement Table S10).

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

351

352 **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	Intraparenchymal	175/185 (95)	56/56 (100)	231/241 (96)
		Intraventricular	149/175 (85)	52/56 (93)	201/231 (87)
		Subarachnoid	40/175 (23)	4/56 (7)	44/231 (19)
			23/175 (13)	3/56 (5)	26/231 (11)
	Spinal	Intra-medullary	16/168 (11)	2/3 (67)	18/171 (12)
		Extra-medullary	3/16 (19)	1/1 (100)	4/17 (24)
			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)	

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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, cerebral/cerebellar etc.) remains unclear.

367 ² Most symptomatic cases reported more than one neurological sign/symptom, therefore column totals are larger than N=125 or 100%, respectively.

368 ³ Signs/symptoms described as: "meningeal signs, neck stiffness, meningism, neck rigidity"

369

TABLE 3. Neurological signs/symptoms stratified by cyst(s) location, number, radiological characteristics and stage¹

			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)		39/91 (43)		30/101 (30)	
Only intraventricular ²			2/13 (15)	p<0.001	12/14 (86)	p=0.01	10/14 (71)	p<0.001
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)		22/34 (65)		16/34 (47)	
	Degenerative stage ⁴		82/116 (71)	p<0.005	47/107 (44)	p=0.06	46/95 (48)	p=0.84
	Calcified stage		15/23 (65)		9/24 (38)		10/24 (42)	

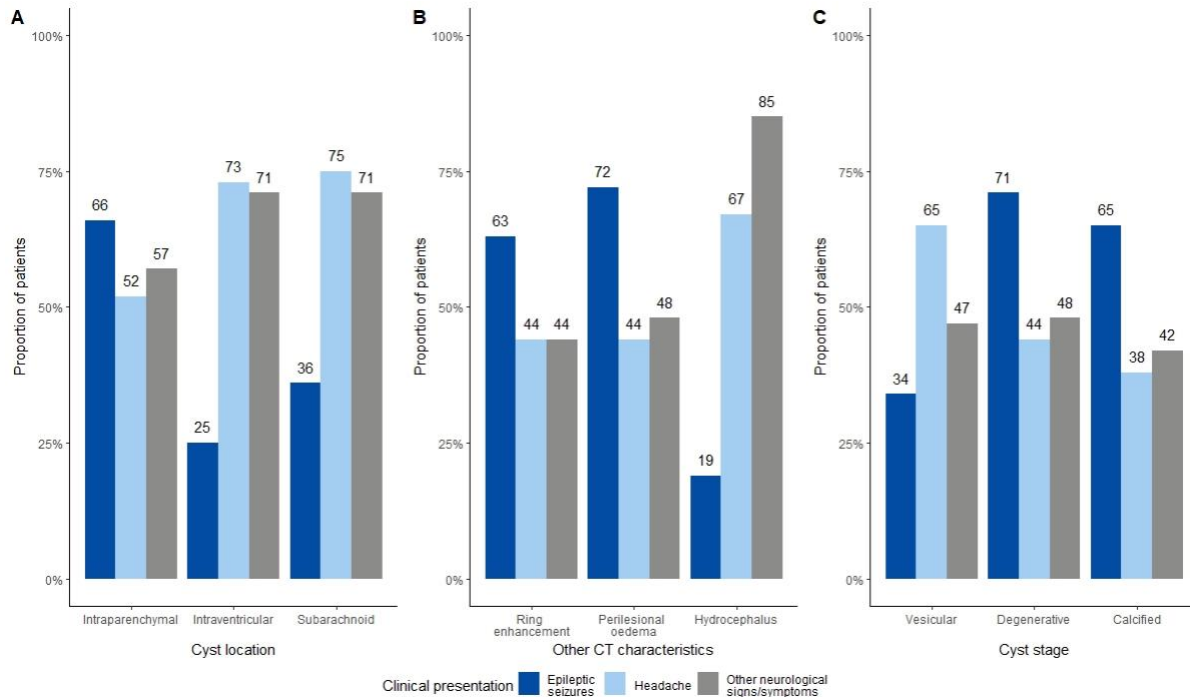
¹ Only patients with detailed information on stage of the cyst(s) were included (published and unpublished cases). Data refer to the known information on epileptic seizures, headache and other neurological signs/symptoms by group categorised in the left hand column (e.g. intraparenchymal cysts). "n" 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



346

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

350

351 Discussion

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

357

358 *Origins of infection*

359

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

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

375

376 *Clinical characteristics and related findings on neuroimaging*

377

378 The sites and stages of cysts influences how patients with NCC present. With regards to site, most
379 symptomatic patients with intraparenchymal cysts presented with epileptic seizures compared to
380 patients with extraparenchymal cysts who were more likely to present with non-specific symptoms like
381 headache. Patients with extraparenchymal cysts were significantly older at diagnosis. This may be
382 because patients infected at an older age were more likely to develop extraparenchymal NCC e.g. due
383 to comorbidities and immunological factors or because symptoms were less specific and therefore
384 diagnosis was made at a later stage.³⁵ These findings, i.e. patients with extraparenchymal lesions being
385 older and showing more non-specific signs/symptoms, concur with NCC data published from Mexico.⁵
386 The number of patients with autochthonous cases was rather low so it was difficult to draw conclusions
387 on disease presentation in comparison to patients you were infected in Latin America, Asia or Africa.
388 Ring enhancing lesions and those with perilesional edema also seemed to predispose to presentation
389 with epileptic seizures. However, although epileptic seizures occurred frequently under those
390 conditions, around half of the cases were also accompanied by other neurological signs and symptoms,
391 including headache. The latter, however, was frequently reported in extraparenchymal NCC
392 (intraventricular and subarachnoid NCC) and when hydrocephalus was present. Looking at cyst stage,
393 headache prevailed in the vesicular stage, where little to no inflammation was evident on radiology, the
394 pathophysiology of headache under these conditions is not clear (ASW unpublished data), whereas
395 epileptic seizures were the predominant neurological symptom during the degenerative stage of the
396 cyst(s)

397 It is well established that clinical manifestations of NCC can vary from completely asymptomatic
398 infection (54% of NCC patients in a study of Monteiro de Almeida et al.³⁶) to severe disease and death.^{2,37}
399 The major determinants of the characteristics of symptomatic NCC are the number of cysts, their
400 location, their stage and the degree of inflammation.^{35,38} It has been shown previously that NCC can
401 mimic almost any neurological disorder³⁹, but to date neurological signs/symptoms other than epileptic
402 seizures or headache are thought to occur in the minority of patients.¹ In concordance with previous

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

411 Regarding publications included in our study, the classification of neurological signs/symptoms other
412 than epileptic seizures and headache was challenging as description of signs/symptoms could be vague
413 and their origin remaining uncertain (see Table 3). Remarkably, in our study, impaired cognitive
414 function appeared to be one of the most frequent other neurological signs. In the included publications,
415 EEG was rarely performed and predominantly only when epileptic seizures were present. Therefore,
416 non-convulsive seizures that could account for impaired cognitive function may not have been
417 identified. A high proportion of cognitive decline (87.5%), dementia (12.5%) or altered mental state
418 (28%) in NCC patients has also been observed in previous studies.^{1,41,42}

419

420 *Special considerations*

421

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

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

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

442

443 *The value of serology and neuroimaging*

444

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

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

470

471 *Treatment of symptomatic patients with neurocysticercosis*

472

473 In the IDSA/ASTMH guidelines, different recommendations for anthelmintic treatment are given for
474 different manifestations of NCC.⁵³ Surgical removal and/or ventricular shunting in the case of increased
475 intracranial pressure is recommended for patients with intraventricular cysts. For patients with NCC-
476 related hydrocephalus or diffuse cerebral edema, corticosteroid therapy without anthelmintics is
477 recommended. For patients with one or two intraparenchymal cysts, 15mg/kg/day albendazole is
478 advised for 10-14 days with treatment extended if no effect in terms of cyst resolution is shown; for
479 patients with more than two viable intraparenchymal cysts it is recommended to combine albendazole
480 with praziquantel 50mg/kg/day is recommended.⁵³ Generally, treatment recommendations do not differ
481 for children and adults, apart from an adjustment of anthelmintic drug dosage. In our dataset, which
482 includes many cases that were diagnosed and treated before the above guidelines were published in
483 2018, approaches to treatment were extremely varied and longer durations and higher dosages were
484 given to patients with more severe manifestations or to non-responders. This reflects the importance of
485 having clear consensus guidance for treatment in order to improve safety and efficacy, and to better
486 understand treatment outcomes.

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

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

511

512 *Recommendations for diagnosis and treatment of neurocysticercosis*

513

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

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

529

530 *Neurocysticercosis in the context of migration and travel medicine*

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

539

540 *Strengths and limitations*

541

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

559

560 **Conclusions**

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

571

572 **Author Contributions:** Conceptualization, A.A., D.S., V.S., M.K. and A.S.W; methodology, A.A., D.S.; software,
573 A.A., D.S.; validation, A.A., D.S., V.S., M.K., A.S.W.; formal analysis, A.A., D.S.; investigation, A.A., D.S.; resources,
574 A.S.W.; data curation, D.S.; writing—original draft preparation, A.A., D.S., M.K., V.S., A.S.W.; writing—review and
575 editing, all authors; visualization, A.A., D.S.; supervision, A.S.W; project administration, A.A., D.S.; funding
576 acquisition, A.S.W. All authors have read and agreed to the published version of the manuscript.

577 **Funding:** A.A. received a “Short Term Scientific Mission” grant from CYSTINET (Cost Action TD1302) and travel
578 grants to CYSTINET conferences. PLC is supported by the University College London Hospitals Biomedical
579 Research Centre. NFW was supported by a UK National Institute for Health Research (NIHR) Academic Clinical
580 Lecturership. AA was partially funded by the German Federal Ministry of Education and Research (BMBF) [The
581 Lancet One Health Commission 01KA1912].
582

583 **Data Availability Statement:** In this study, we report data from mostly published cases. The references to these
584 cases are given in the supplementary material and the extracted data were published under the following doi:
585 10.14459/2021mp1638110

586 **Acknowledgments:** The authors gratefully acknowledge the contribution of CYSTINET to this work, in terms of
587 financial support of meetings as well as for networking. A special thanks goes to all CYSTINET members for their
588 support and collaboration. Furthermore, we would like to thank and remember our colleague and friend Prof. Dr.
589 Teresa Garate. Teresa Garate headed Working Group 2 of CYSTINET, together with Andrea Winkler and Pierre
590 Dorny. We remain deeply saddened by the unexpected loss of our dear and respected colleague.

591 **Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study;
592 in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish
593 the results.

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