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SHORT REPORT
Human cysticercosis in Portugal: long gone or still contemporary?

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SUMMARY

Cysticercosis, a leading cause of acquired epilepsy in developing countries, has been controlled or eradicated in industrialized countries. This paradigm has recently been challenged, with human neurocysticercosis (NCC) being increasingly diagnosed in these countries. In order to assess the NCC burden in Portugal, a retrospective study on NCC hospitalizations (2006–2013) was conducted based on the national database on hospital morbidity: 357 hospitalized cases were detected. NCC was most frequent in the following age groups: 20–64 years ($n = 197$, 55·2%) >64 years ($n = 111$, 31·1%), and <20 years ($n = 49$, 13·7%). In the Norte and Centro regions cases tended to be older than in the Lisboa and Vale do Tejo Region. The results raise concerns for imported and autochthonous disease, suggesting the Lisboa and Vale do Tejo Region, due to its higher frequency of cases at younger ages, as a priority for research and intervention, and further suggest that NCC should be under surveillance (notifiable). The National Observatory of Cysticercosis and Taeniasis has been established and will define NCC cases as well as monitoring and surveillance.

Key words: Neurocysticercosis, Portugal, surveillance.

Cysticercosis results from the ingestion of *Taenia solium* eggs directly via the faecal–oral route or contaminated food. Human tapeworm carriers who were infected after ingesting raw or undercooked pork meat contaminated with cysticerci develop intestinal taeniasis and shed *T. solium* eggs in the faeces. The larvae released from the ingested eggs develop into cysticerci that lodge mainly in central nervous system (CNS) and striated muscle. In humans, the CNS is the most frequent localization of cysts; the resulting disease condition is neurocysticercosis (NCC) [1]. Humans may become infected at any age and may acquire cysticercosis by ingesting *T. solium* eggs released by themselves or by other tapeworm carriers living with them or involved in the preparation of their food. The incubation period is long; therefore the diagnosis may be made many years after the infection has occurred [2].

NCC is clinically heterogeneous, ranging from asymptomatic infection to severe and incapacitating diverse clinical manifestations, such as seizures, hydrocephaly, stroke, dementia, and other neurological signs [3, 4]. Most symptoms are the direct result of

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the inflammatory process that accompanies cyst degeneration [5]. The degeneration process is presumed to occur many years after infection, which is why age at diagnosis is an important epidemiological variable. Recent onset of seizures in otherwise healthy teenage, young adult, or middle-aged individuals arriving from endemic regions suggests NCC [5]. Since the incubation period is usually shorter in children, the absence of NCC cases in young adults and children indicates that the life-cycle of the parasite is very unlikely to occur in these groups. On other hand, a higher than expected frequency of cases in young people in one region may suggest an active life-cycle, clustering around a *T. solium* host or imported cases.

This zoonosis, a leading cause of acquired epilepsy in developing countries, has been controlled or eradicated in industrialized countries due to significant improvements in sanitation, pig rearing and slaughterhouse control systems [4]. Nevertheless, NCC, a preventable disease, is gradually becoming recognized as an emerging public health problem in high-income countries [6, 7].

In Portugal, cysticercosis was considered highly prevalent before 1975. Thereafter, improved sanitation and industrialized pig production under veterinary control made Portugal officially free of pig cysticercosis and since then diagnosed human cases have been considered mainly imported (Statistics Portugal, www.ine.pt). As in most European countries, there is no disease notification or surveillance for NCC. A national burden for NCC is virtually unknown. Both autochthonous and imported human cysticercosis emergence is plausible in face of the scarce and old national data available and increased NCC reporting in different industrialized countries.

To assess NCC burden and characteristics at the national level, a retrospective study on NCC hospitalizations was conducted based on the national database on hospital morbidity resulting from National Health Service (NHS) hospital episodes, provided anonymously by the Central Administration of Health System (ACSS). This database includes all NHS hospitalizations (126 hospitals) and has information on demographics, diagnostic and procedural codes, length of stay and discharge status. It does not include hospitalizations in private or military sectors. Upon hospital discharge, specifically trained medical coders (doctors) carry out the coding of diagnosis and procedures, according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), based on the diagnosis assigned by the attending physician, and the medical records and charts.

Consecutive NCC hospitalizations were obtained from 2006 to 2013, using ICD-9-CM code 123·1 (cysticercosis). Since there is no ICD-9-CM diagnostic code specific for NCC, resulting records were manually checked and considered as NCC hospitalizations if there was a supporting diagnostic or procedural code consistent with a manifestation of neurological disease. The following supporting coded diagnoses were identified: encephalitis; other CNS infection; epilepsy; convulsions; headache, including migraine; acute cerebrovascular disease; other and ill-defined cerebrovascular disease; transient cerebral ischaemia; syncope; anxiety disorders; delirium, dementia, and amnestic and other cognitive disorders; obstructive hydrocephalus; cerebral cysts; intracerebral haemorrhage; mood disorders and unspecified psychosis. All considered NCC hospitalizations had procedural codes of neuroimaging studies (computed tomography scanning and/or magnetic resonance imaging). Other supporting coded procedures identified were: insertion, replacement or removal of extra-cranial ventricular shunt; lumbar puncture; electroencephalogram and brain biopsy.

Duplicate records in the database, due to readmission or transference between hospitals, were removed. Gender, date of birth and residence were used as identity proxy markers for this purpose and resulting records were manually checked for coherence before final removal. Variables included gender, age, year of hospitalization, residence details (municipality, district, region), and related diagnosis.

A descriptive analysis was performed, using the usual indicators of frequency synthesis and hypothesis testing, a 5% significance level was considered. Regarding the residence details of hospitalized cases, specific age- and gender-adjusted frequency rates/100 000 inhabitants were calculated by the direct standardization method. Reference population was obtained from the population Census 2011 (http://censos.ine.pt/xportal/xmain?xpid=CENSOS&xpgid=censos_ficheirosintese, Statistics Portugal, www.ine.pt). Based on residence details, the geographical regions considered were, from north to south: Norte, Centro, Lisboa and Vale do Tejo, Alentejo, and Algarve. The age groups considered were <20, >64 and 20–64 years, roughly reflecting those born after and before the full implementation of the sanitary and industrialized pig production politics and

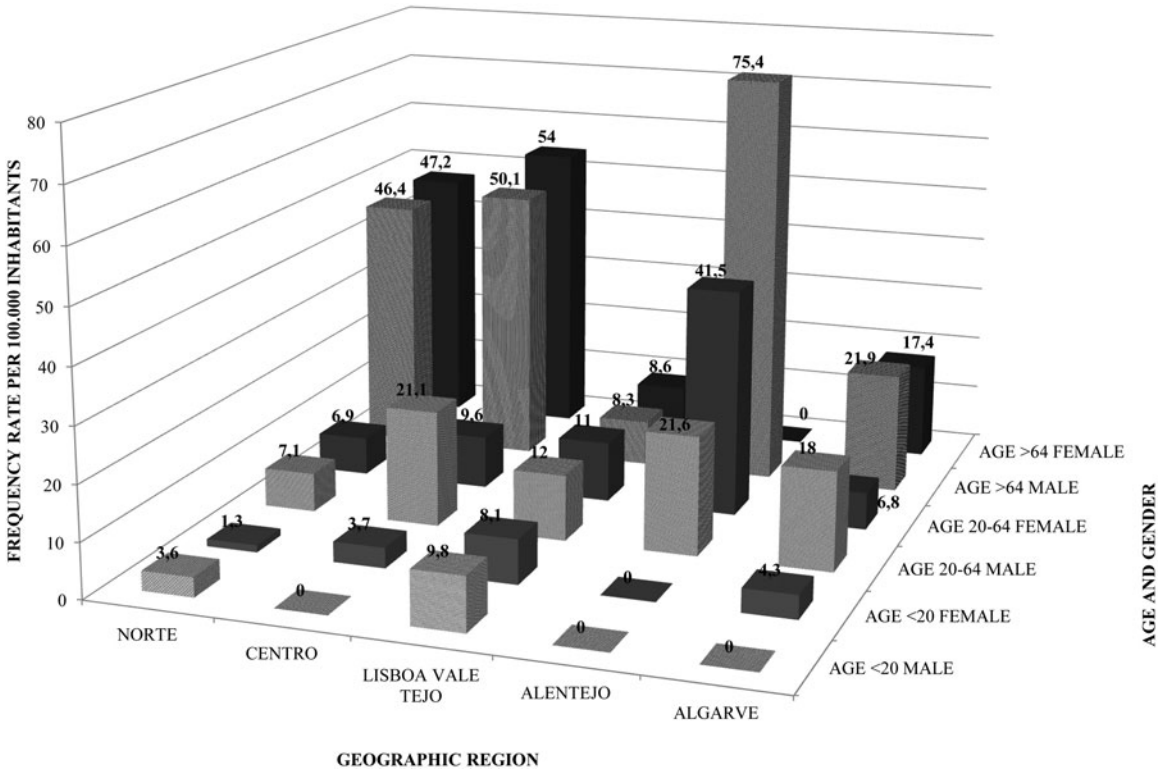

Fig. 1. Neurocysticercosis in Portugal 2006–2013: age- and gender-adjusted distribution within the five geographical regions.

measures in Portugal and those mainly of working age, which also includes immigrants of working age. Data were analysed using Microsoft Excel (Microsoft, USA) and IBM SPSS Statistics v. 21 (IBM Corp., USA).

Between 2006 and 2013 there were 357 hospitalized NCC cases in Portugal. Annual frequency of cases remained stable (mean 45), ranging from a minimum of 35 in 2007 to 55 in 2008, corresponding to 0·33–0·52 cases/100 000 inhabitants per year. NCC was most frequent in the following age groups: 20–64 years (197, 55·2%), >64 years (111, 31·1%), and <20 years (49, 13·7%) of hospitalized cases. The male to female ratio was 0·97.

Considering geographical distribution of cases in absolute numbers, most cases were in the Lisboa and Vale do Tejo Region ($n = 200$, 56·0%) followed by the Norte Region ($n = 87$, 24·3%).

In the Norte and Centro regions cases tended to be older than in the Lisboa and Vale do Tejo Region. Age- and gender-adjusted rates were higher in the Lisboa and Vale do Tejo Region for those aged <20 years compared to the other regions: 9·8/100 000 inhabitants in males and 8·1/100 000 inhabitants in females. Age- and gender-adjusted rates were higher in the Norte and the Centro regions for those aged >64 years compared to the Lisboa and Vale do Tejo Region: 46·4/100 000 inhabitants in males (22 cases) and 47·2/100 000 in females (32 cases) in the Norte Region; 50·1/100 000 inhabitants in males (nine cases) and 54·0/100 000 in females (14 cases) in the Centro Region; 8·3/100 000 inhabitants in males (11 cases) and 8·6/100 000 in females (16 cases) in the Lisboa and Vale do Tejo Region (Fig. 1). The comparatively high rates observed in the Alentejo and the Algarve regions correspond to low absolute numbers of cases in low population density areas (Alentejo: three cases in the 20–64 years group and one case in the aged >64 years group; Algarve: six cases in the >64 years group).

NCC cases were associated with other neurological diagnoses at different ages. Stroke (40, 11·2%) and dementia (21, 5·9%) were significantly more frequent in older ages (mean age 75·6 *vs.* 43·4 and 78·0 *vs.* 45·5 years, Student's t test, $P < 0·001$) while headaches (20, 5·6%) were more frequent at younger ages (mean age 34·4 *vs.* 48·2 years, Student's t test, $P = 0·003$). Epilepsy (157, 44%), a classical NCC manifestation, was not statistically associated with age (mean age 44·9 *vs.* 49·5 years, Student's t test, $P > 0·05$),

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nor was obstructive hydrocephalus (19, 5·3%; mean age 45·6 *vs.* 47·5 years, Student's *t* test, $P > 0{\cdot}05$). No statistically significant gender differences were observed (χ^2, $P > 0{\cdot}05$).

Human cysticercosis is increasingly considered an emerging public health issue in high-income countries, namely in European countries [6, 8]. Cysticercosis virtually disappeared from industrialized countries when the role of porcine cysticercosis was understood and strict control measures were implemented. However, increased migration and international travel from endemic regions favour not only disease importation but also autochthonous disease that may affect communities with poor hygiene conditions enabling human-to-human parasite spread in the absence of travel to endemic regions. Zammarchi *et al.*, in a recent systematic review of the literature on cysticercosis and *T. solium* taeniasis observed in Europe, highlight the increasing disease importation: 38·3% of cases were imported (324 out of 846 total cases in Europe) [9]. Autochthonous disease data is, however, biased by data from the Norte Region of Portugal from the 1980s and early 1990s (366/522 total autochthonous cases in Europe) corresponding to a past sustained endemic focus [9,10]. This is thought to have changed completely due to improved sanitation and pig production industrialization and control. In 2009, 98·5% of domestic households had piped potable water and 84% had a sewage system, compared to <66% and 17%, respectively, in 1972 (Statistics Portugal, www.ine.pt). Human cysticercosis is thought to have evolved towards an imported disease, as documented in sporadic case reports and small case-series (G. Januario *et al.*, personal communication). Still, three autochthonous cases have been reported recently in native Portuguese without a recognized travel epidemiology (in a male hunter aged 55 years and two females aged 39 and 57 years), suggesting ongoing human-to-human transmission (S. Chan *et al.*, personal communication) [11, 12].

The analysis of the 357 NCC hospitalizations in Portugal during 2006–2013, corresponding to 0·33–0·52 cases/100 000 inhabitants per year, indicates a stable annual disease frequency and a burden which demands monitoring by the public health authorities.

It appears to reveal two apparently distinct epidemiological scenarios: (1) one in the Lisboa and Vale do Tejo Region where >50% of the hospitalizations occurred, concerning mainly the younger age groups; and (2) one in the Norte and Centro regions, mainly in older individuals and possibly still related to the past endemic focus in this region. Historical cultural and social links contribute to past and present increasing immigration from developing countries, namely South America (Brazil) and Africa (Cape Verde, Angola, Guinea–Bissau). The Lisboa and Vale do Tejo Region accounts for the majority (51·6%) of immigrants, but the Norte (13·1%), Centro (13·9%) and Algarve (13·2%) regions are also well known for their settled immigration communities (Statistics Portugal, www.ine.pt).

This geographical distribution does not reflect the place of infection, due to the nature of the disease, i.e. long incubation periods and human mobility, but identifies areas where further in-depth research is needed, namely utilizing epidemiological field studies to understand the underlying drivers, while bearing in mind the impact of imported cases and the possibility of emerging autochthonous transmission, requiring human, animal and environmental determinant research. Such a number of cases occurring in young people in one region may suggest an active life-cycle, clustering around a *T. solium* host or imported cases. As such, as a starting point, this study indicates that efforts should concentrate on the Lisboa and Vale do Tejo Region.

Moreover, it emphasizes the relevance of NCC surveillance, making it a reportable disease in Portugal and in industrialized countries in general. Physicians need to be aware that a new NCC diagnosed patient could mean that someone in the patient's immediate environment is a tapeworm carrier. Notification also has the major advantage of providing accurate quantification of the incidence and prevalence, thus enabling the launching of appropriate epidemiological interventions and the rational use of resources in order to interrupt the chain of transmission. This includes identifying and treating sources of contagion (namely tapeworm human carriers); identifying and treating other exposed contacts; health education and promotion, namely frequent hand washing, and improved hygiene and sanitation; and sustained veterinary pig control policies and practices.

The national database on hospital morbidity should be included in a disease surveillance strategy, since it can be a valuable source for retrospectively assessing and monitoring NCC hospitalizations, which represent the most severe illness spectrum in the absence of a notification system. Moreover, it enables the detection of possible geographical hotspots such as the Lisboa and Vale do Tejo in this case. An advantage of the national database is that the data are systematically collected, standardized and not compromised by

underreporting, albeit this is not done for epidemiological purposes. Epidemiological variables such as nationality, risk exposure and travel data or migrant data are not collected and therefore information on probable geographical region of infection cannot be obtained. Analysis of related neurological diagnosis, although illustrative and interesting, needs to take into account that hospitalization diagnostic codes may not represent the distribution of disease manifestations experienced by individual patients, reflecting those considered most relevant in light of the main diagnosis and cause of admission. For example if a patient has headaches due to obstructive hydrocephalus, both these diagnoses or only obstructive hydrocephalus may be coded regarding the probable cause of the symptoms, severity and need for specific procedures. On the other hand, NCC may be asymptomatic and diagnosed during the work-up of stroke, dementia or concussion (incidental diagnosis). Still, this study aims to present a global picture of NCC in Portugal from a public health perspective, not only clinically acute cases.

NHS hospitalizations do not capture all NCC cases. NHS emergency department visits that do not result in admission are not captured nor are outpatient follow-ups. NHS hospitalizations also do not include healthcare provided in the private or military sectors, although healthcare in Portugal is mainly NHS based. There is no other data source in Portugal that can provide information on the national NCC burden; information otherwise available is very scarce and consists of sporadic hospital-based case reports and small case-series. Despite its limitations, this database allows for timely nationwide data that would be otherwise unfeasible or logistically cumbersome to obtain, enabling a comprehensive addition to the surveillance system. Therefore, at present, NCC hospitalizations provide the best and only disease estimates available.

The Portuguese Taeniasis and Cysticercosis Observatory (PTCO) has recently been founded (2016), supported by the Directorate General of Health, as a consequence of a need for increased awareness, surveillance and control of this non-notifiable neglected zoonosis in Portugal that continues to take its toll of the population. It involves a human and animal health, public health transdisciplinary approach and collaboration at governance, academic and professional levels, in a One-Health perspective. This paper results from the first activities of the PTCO, aiming at better characterizing the human disease burden at the national level in order to identify possible hotspots for subsequent in-depth analysis and intervention. The PTCO is committed to further identify and fill in the knowledge and evidence gaps concerning the burden and epidemiology of cysticercosis in Portugal.

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A list of Action key members of the European Network on Taeniosis/Cysticercosis, CYSTINET – COST Action TD1302 can be found at http://www.cystinet.org/the-action/organisation/).

DECLARATION OF INTEREST

None.

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