Neurocysticercosis Infection and Disease – A Review

Acta Tropica 166 (2017) 218–224

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Neurocysticercosis infection and disease–A review

Lucy B. Gripper, Susan C. Welburn*

Division of Infection and Pathway Medicine, Edinburgh Infectious Diseases, Edinburgh Medical School, Biomedical Sciences, The University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, UK

ARTICLE INFO

Article history:
Received 25 August 2016
Received in revised form
15 November 2016
Accepted 15 November 2016
Available online 20 November 2016

Keywords:
Neurocysticercosis (NCC)
Extra-parenchymal neurocysticercosis
Zoonoses
Neglected tropical diseases
Taeniasis
Cestode
Taenia solium
Lateral flow assay
Epilepsy

ABSTRACT

Neurocysticercosis (NCC) is the most common parasitic disease of the human central nervous system (CNS), a pleomorphic disease with a diverse array of clinical manifestations. The infection is pleomorphic and dependent on a complex range of interconnecting factors, including number and size of the cysticerci, their stage of development and localisation within the brain with resulting difficulties in accurate diagnosis and staging of the disease. This review examines the factors that contribute to the accurate assessment of NCC distribution and transmission that are critical to achieving robust disease burden calculations.

Control and prevention of *T. solium* transmission should be a key priority in global health as intervention can reduce the substantial healthcare and economic burdens inflicted by both NCC and taeniasis. Surveillance systems need to be better established, including implementing obligatory notification of cases. In the absence of reliable estimates of its global burden, NCC will remain-along with other endemic zoonoses, of low priority in the eyes of funding agencies–a truly neglected disease.

Contents

* Corresponding author.
E-mail address: Sue.Welburn@ed.ac.uk (S.C. Welburn).

http://dx.doi.org/10.1016/j.actatropica.2016.11.015

1. Introduction

Neurocysticercosis (NCC) is the most common parasitic disease of the human central nervous system (CNS) (Del Brutto, 2012). Caused by the larval form of the cestode, *Taenia solium*, commonly referred to as the 'pork tapeworm' (Fogang et al., 2015), NCC is not to be confused with 'taeniasis', the condition resulting from adult tapeworm infection. Human or porcine NCC originates from the ingestion of food or water that is contaminated with *T. solium* eggs; these hatch within and then penetrate the intestine, following which, a period of widespread tissue dissemination occurs. Multiple body tissues may be invaded, including the eyes, skin and muscles (WHO, 2016), however the larvae display a strong affinity for the CNS (Sinha and Sharma, 2009). NCC has a diverse array of clinical manifestations, depending on a complex range of interconnecting factors, including the number and size of the cysticerci present, their stage of development and localisation within the brain with resulting difficulties in accurate diagnosis and staging of the disease (Takayanagui and Odashima, 2006).

Aristotle was aware of NCC in 424 BCE, describing the presence of muscle cysts, compared to hailstones in appearance, evident in certain porcine diseases (Del Brutto et al., 1998). Until the development of CT and MRI scans in the 20th century, knowledge of NCC was very limited, as the majority of diagnoses were based on clinical manifestations visible externally to the naked eye, such as presence of subcutaneous nodules, or on post-mortem observations made at autopsy (Garcia et al., 2002). This advance in diagnostic capabilities was a watershed in our understanding of NCC, redefining prognoses. Previously only the severest cases had been apparent to clinicians, giving a distorted view of disease severity; advances in scanning allowed for the diagnosis of previously undetected milder cases and further consideration was given to the spectrum of presentations that existed (Garcia et al., 2002).

1.1. Parasite lifecycle

T. solium belongs to the class Cestoda, one of the largest and most successful groups of parasitic tapeworms, comprising approximately 5000 species. The family Taeniidae is divided into three genera: *Taenia* (sub-divided into *Taenia* and *Versteria*; Nakao et al., 2013) of which *T. solium* is a species, and *Echinococcus* (Bobes et al., 2014).

The lifecycle of *T. solium* is complex and may result in a range of pathologies, affecting both pigs and humans. Humans are the only definitive hosts, within which the tapeworm can complete its lifecycle and exist in adult form, however both humans and pigs have been documented as intermediate hosts, in which the tapeworm eggs can develop up to the metacestode larval stage (Coral-Almeida et al., 2015). Dogs have also been implicated as intermediate hosts in Asia (Ito et al., 2002).

1.2. Typical lifecycle of T. solium

Human NCC, porcine NCC and dog NCC are mainly due to direct contact with human faeces. Humans become infected most commonly through the ingestion of food or water contaminated with *T. solium* eggs; pigs and dogs through scavenging human faeces. Eggs come from an adult tapeworm that has reached maturity in the small intestine of a human host entering the environment within human faeces; one adult tapeworm can expel a minimum of 100,000 eggs per day. Serological studies in endemic areas have shown that eggs can be distributed in the environment at large distances from the infected individual (Lescano et al., 2009). It has also been suggested that humans may be able to autoinfect themselves (Kobayashi et al., 2013)

In the host intestinal tract, eggs become uncoated liberating the enclosed larvae, known as oncospheres. These penetrate the intestinal wall and are transported in the bloodstream to various tissues of the body, including the brain, eyes, skin and muscles, where they are deposited (Del Brutto, 2012). Within these tissues oncospheres differentiate and develop into metacestodes, which undergo multiple stages of development and establish as cysticerci. The first stage is known as the 'viable or vesicular stage' in which a membrane develops around each oncosphere, forming a vesicle that contains clear fluid surrounding the parasite head, or scolex. Depending on the surrounding environment, and the nature of the immune response their presence elicits, the cysts may remain at this stage for months or even years, before they begin to degenerate. The 'colloidal stage' marks this transition, whereby the scolex shows signs of deterioration and the vesicular fluid begins to appear turbid. Following this, the vesicular fluid becomes gradually more opaque and the cyst begins to calcify, eventually terminating its evolution as non-viable calcified nodule (Coral-Almeida et al., 2015).

The lifecycle is completed when humans ingest undercooked pork containing viable cysticerci. Digestive enzymes in the small intestine cause the scolices to evaginate from the cyst vesicle and attach to the wall of the intestine using powerful suckers and hooks. Here, the tapeworm matures to adulthood, at which point egg-containing sections of the tapeworm body, called 'gravid proglottids', are released in the host's faeces (Del Brutto, 2012). This part of the tapeworm lifecycle accounts for the disease taeniasis only; it is a common misconception that eating undercooked pork can result in cysticercosis.

2. Epidemiology

Despite being one of the most prevalent parasitic disease of the human CNS (Fabiani and Bruschi, 2013), NCC remains a neglected tropical disease, recognised in 2010 by the World Health Organisation (WHO, 2016). Despite its substantial global impact, in terms of both disease and economic burden, there are limited data for accurate assessment of distribution and transmission (Crompton and Peters, 2010). However, awareness of cysticercosis is increasing (Ito and Budke, 2014) and bodies such as WHO have put forward improved strategies for the control of both taeniasis and cysticercosis (WHO, 2016).

2.1. Endemicity of NCC

NCC particularly affects countries burdened by poverty, as lack of adequate sanitation and inaccessibility of clean water supplies increase contamination of both food and water with human faeces containing *T. solium* eggs. Countries where NCC is endemic may also have high numbers of free-roaming pigs that are exposed to human faeces, leading to increased incidence of porcine NCC (Coyle et al., 2012). Once established within a population, the taeniasis-cysticercosis complex shows high epidemiological stability, due to a number of factors, including the durability of the eggs and the potential for a single tapeworm to infect multiple individuals including the tapeworm carrier (Kobayashi et al., 2013); this has contributed substantially to logistical difficulties in infection control (Fabiani and Bruschi, 2013).

Areas endemic for NCC include Latin America, Africa, South East Asia, India, China and Nepal (Fabiani and Bruschi, 2013). Differences are observed the clinical and radiological presentations of NCC between countries in different continents. Patients in India show higher frequency of symptomatic NCC caused by a single, isolated, parenchymal cysticercus, compared to patients in Latin America, who more frequently exhibit multiple cysticerci in the ventricles

or subarachnoid space (Bobes et al., 2014). This may reflect genetic dispositions associated with varying presentations between geographical areas and differing lifestyles among human populations (Yanagida et al., 2014), where the infection was acquired (Yanagida et al., 2010), as well as genetic differences between parasite populations (Ito et al., 2016).

Despite a lack of accurate prevalence data, various studies have applied statistical methods to approximate disease burden (Coyle et al., 2012). These burden estimates indicate the relative impact of the disease in certain areas of the world, but would be much improved if based on population-based data generated from large-scale studies and improved in-country, surveillance and reporting systems-few of which currently exist (Martins-Melo et al., 2016). Multiple obstacles lead to high variability between individual studies, preventing the acquisition of accurate epidemiological data for NCC; these include inadequacy of current assays leading to missed diagnoses and subsequent underestimations, as well as discrepancies between studies as to whether or not to include cases involving calcified cysts in prevalence calculations as well as resourcing.

2.2. Increasing incidence in Low and Middle Income Countries (LMIC)

There have been observations of increasing incidence of NCC in high income countries, particularly in the USA, where over 5000 infected patients have been reported in recent years (Sorvillo et al., 2011), as well as in Canada and Europe (Coyle et al., 2012) attributed to increasing rates of immigration. The great biotic potential of tapeworms represents a significant risk of sustained propagation within these newly-established populations; this risk is compounded by the relative inexperience in handling such parasitic infections.

3. Clinical presentation

The pleomorphic nature of clinical presentations associated with NCC can be attributed to many factors. The parasite load, dependent on both the size and number of cysticerci, is an important determinant of symptomatology; high loads are associated with increased risk of obstruction and corresponding rises in intra-cranial pressure (ICP) as well as induction of significant inflammatory responses (Singhi and Suthar, 2015). In very severe cases, involving numerous cysts with associated inflammation, an encephalitic state can occur with diffuse cerebral oedema; such cases have a very poor prognosis (Kimura-Hayama et al., 2010).

The stage of cysticercus development is a crucial factor in the control of immune interactions. It is thought that viable cysts initiate a complex immune evasion response, allowing them to exist undetected in the body; this may persist for a prolonged period of time, with immune-mediated symptoms sometimes being delayed for several, or as many as 10 years (Kimura-Hayama et al., 2010; Yanagida et al., 2010).

Development of symptoms is generally associated with the immune system overcoming such evasion mechanisms and initiating subsequent immune responses against the degenerating cyst, leading to systemic effects and a corresponding clinical profile (Garcia et al., 2010). This process may be accelerated by anti-helminthic drug treatment, and clinicians are cautious when prescribing such medication to patients with high parasite loads (Tuero et al., 2015).

Finally, cyst location is a key determinant of clinical presentation, with clusters of symptoms showing patterns of association with affected areas of the CNS. In general, cyst location is broadly classified as either parenchymal, within the functional tissues of the brain, or extra-parenchymal, which encompasses the remaining locations within the CNS (Garcia et al., 2002).

3.1. Parenchymal NCC

The brain parenchyma is most commonly infected with NCC (Bansal et al., 2014) with high rates of cyst deposition occurring at junctions separating grey matter from white matter; this is thought to be due to accumulation of metacestodes in the small terminal blood vessels that converge here. Parenchymal disease generally has a more favourable prognosis than extra-parenchymal, with seizures and headaches, tending to resolve independently with time, being the most consistently reported manifestations (Singhi and Suthar, 2015). Psychiatric symptoms have been reported on occasion, however the majority of studies have found this to be a rare occurrence, presenting in approximately 5% of NCC cases (Carabin et al., 2011). Importantly, it should be noted that the burden of NCC-associated disease is commonly overestimated, as asymptomatic or only mildly symptomatic patients very rarely present at neurology clinics; as many as 50% of NCC cases had no history of symptoms (Carabin et al., 2011).

The link between NCC and epilepsy is implied to be a causal relationship by the majority of studies, but to assume causality-not simply high rates of co-occurrence-is unwise without further analysis of the discrepancies that are evident in existing studies. Definitions as to what distinguishes epilepsy from seizures need to be more clearly established; by definition 'epilepsy' is the occurrence of recurrent and unprovoked seizures, therefore seizures related to active cysticerci would be classified as 'acute symptomatic seizures', which are not synonymous with epilepsy (Carpio and Romo, 2014). Terminology aside, there still exist further issues with some of the conclusions drawn from certain aspects of the literature on this topic. Several reports use seropositivity inferred from enzyme-linked immuno-electrotransfer blot (EITB) assay as a definitive indicator of active NCC infection, despite both the accepted inaccuracies of this method and the fact that presence of *T. solium* antibodies does not conclusively specify active disease, nor CNS involvement; such work may therefore misrepresent the epidemiology of the epilepsy-NCC relationship (Carpio and Romo, 2014). There also exists an evident selection bias in certain studies, where sample populations have high rates of both epilepsy and NCC; an incidental relationship must first be considered, as well as the potential for genetic predisposition in certain geographical areas showing high rates of familial aggregation of NCC (Carpio and Romo, 2014). Whilst the high co-prevalence of the two conditions certainly provides a strong indication of a causal relationship, these factors highlight flaws in a hypothesis that seems to have been widely accepted.

3.2. Extra-Parenchymal NCC

Clinical manifestations of extra-parenchymal NCC show greater heterogeneity than those associated with parenchymal disease, as a wide range of locations throughout the CNS are included within this broad definition. In general, extra-parenchymal disease has a poorer prognosis than parenchymal, as parasite loads tend to be higher, and growth of individual cysticerci is less restricted and tends to be more irregular; this is associated with higher rates of morbidity and mortality (Tuero et al., 2015).

The most common location of extra-parenchymal NCC is in the subarachnoid spaces and associated meninges (Kimura-Hayama et al., 2010). In severe cases, subarachnoid NCC can trigger mass inflammation in this area, leading to arachnoiditis; this can have multiple effects of significant severity, one example being the development of a hydrocephalic state, in which severe oedema leads to a sharp increase in ICP (Callacondo et al., 2012). Thickening

of the inflamed meninges, along with oedema, may also impact surrounding nerves leading to entrapment of components of the CNS such as the optic chiasm and cranial nerves with an assortment of nerve palsies and visual impairments (Kimura-Hayama et al., 2010). Another mechanism by which hydrocephalus can occur is through the obstruction of cerebro-spinal fluid (CSF) flow, either due to high parasite burden in the subarachnoid space, or through cyst deposition in the ventricular system. Prognosis for subarachnoid disease is further impacted by the occasional development of a proliferating cyst cluster, which forms through the aggregation of abnormal vesicles, known as a 'racemose cyst' (Bansal et al., 2014). Unrestricted growth of a racemose cyst can lead to invasion of various brain spaces, and increases the likelihood of obstruction of CSF pathways or severe inflammatory reactions (Callacondo et al., 2012).

The vascular networks of the brain are similarly affected by obstruction from cysticerci and inflammatory exudates; there may also be direct insult to the blood vessels themselves in the form of vasculitis. Consequential disruption to blood flow can lead to transient or prolonged vascular incidents such as stroke (Callacondo et al., 2012).

Circulating CSF within the subarachnoid space communicates directly with CSF surrounding the spinal column and, as a result, cysts originating in the basal cisterns may follow a gravity-dependent downwards course and disseminate within the spinal meninges. Spinal NCC is rare (Jongwutiwes et al., 2011), with a reported frequency of approximately 0.25%–5.8% of cases (Callacondo et al., 2012) and infrequently presents in isolation without concomitant cranial involvement (Kimura-Hayama et al., 2010). This may present as motor and sensory dysfunction, related to the level at which the lesion occurs (Del Brutto, 2012). Symptoms may include paraesthesia and radicular pain, along the nerve roots into the lower extremities (Singhi and Suthar, 2015).

4. Diagnosis

Accurate diagnosis of NCC is notoriously difficult; available methods are problematic and implementation in resource-poor endemic is patchy. Del Brutto et al. (2001) proposed a set of diagnostic criteria in an attempt to combine aspects of clinical history, neuroimaging and immunological evidence, as well as epidemiological factors, to form defined guidelines for the diagnosis of NCC (see Table 1). This multifaceted approach allows for a diagnosis to be made in the absence of criteria that may be untestable in certain situations.

Using available evidence, a positive diagnosis can be deemed as either 'definitive' or 'probable' based on the weight attributed to the criteria that have been met. While not systematically validated, this approach does allow for otherwise unattainable diagnoses to be made in difficult situations, with a reasonable rate of success (Fogang et al., 2012). For these guidelines to be improved, there is an urgent need for improved diagnostic methods, which achieve high levels of both sensitivity and specificity.

4.1. Neuroimaging

Neuroimaging is the preferred method for NCC diagnosis, using CT and MRI scans it is possible to visualise infecting cysticerci and assess their number and location within the CNS. With experience, the stage of the cyst lifecycle can be defined: viable cysts appear as small, round areas that are easily distinguished from the brain parenchyma, with the scolex appearing as a nodule of high density within the cyst; degenerating cysts are far less well defined and tend to be surrounded by an area of perilesional oedema (Del Brutto, 2012). A typical indicative pattern observed for NCC is the 'starry sky' appearance formed by the presence of multiple cysts at different evolutionary stages (Singhi and Suthar, 2015). CT scans are cheaper and more commonly available, and also show higher sensitivity for detection of calcifications that occur in approximately 50% of patients (Sinha and Sharma, 2009). The higher resolution of MRI scans, permit better distinction of the degenerative stage of cysticerci and can detect parasites located in sites that would be missed by a CT scan, e.g. those located in the posterior fossa, basal cisterns and ventricles (Takayanagui and Odashima, 2006). There are issues with sensitivity, especially for intraventricular and subarachnoid forms, where the cyst fluid and CSF have such similar densities that visualization is unlikely, even when using contrast-enhanced MRI scans (Kimura-Hayama et al., 2010; Singhi and Suthar, 2015).

4.2. Immunological assays

Neuroimaging is expensive and requires both trained personnel and technological resources that are not available in the majority of low income countries in which NCC is endemic. This further reliance on the use of serological testing for the detection of NCC. To date, the lentil lectin purified glycoprotein (LLGP) enzyme-linked immunoelectrotransfer blot (EITB) assay, which uses targeted antigens to detect antibodies to *T. solium* in patient serum, has provided the most consistent results (Fogang et al., 2015; Ito, 2015). This diagnostic test has a reported specificity of 100%, with an overall sensitivity of 98% (Garcia and Del Brutto, 2005); these rates significantly decline in cases where only a single cysticercus is present as the low parasite load elicits a far weaker antibody response, and sensitivity falling as low as 50% (Fogang et al., 2015; Ito, 2015). Antibodies can persist in the serum for long periods after the parasite has been cleared from the body and can be stimulated following exposure to the parasite in the absence of an established infection (Gilman et al., 2012). However, antibody responses have also been shown to diminish within one year of surgery (Ito et al., 1999). In addition, the presence of antibodies in the serum does not inform as to the location of a cyst; testing positive for cysticercus infection is not synonymous with CNS involvement (Fogang et al., 2015; Ito, 2015). These factors mean that the assay results should be interpreted within the clinical context, and strengthen a suspected diagnosis. There has been some debate as to whether NCC is best detected in CSF rather than serum samples (Garcia and Del Brutto, 2005), but a recent comparative study by Sako et al. (2015) showed no differences in sensitivity and specificity between samples of serum and CSF.

New assays are in development that show promising results. Gabriel et al. (2012) reported an ELISA based assay that could detect *T. solium* antigens using monoclonal antibodies prepared from *T. saginata*, indicating the presence of an established infection (as opposed to exposure only). A lateral flow assay (LFA) has recently been developed for the diagnosis and monitoring of extra-parenchymal NCC (Fleury et al., 2016). This assay is based on the use of the monoclonal antibody HP10. This assay, applied to CSF samples correctly identified 34 cases of active extra-parenchymal NCC, and gave negative results for 26 samples derived from treated and cured NCC patients. The assay format is cheaper and is suitable for laboratories that lack the financial resources to support complex diagnostic procedures (Fleury et al., 2016).

4.3. Stool microscopy

Traditional methods such as stool microscopy have been used to visually assess the presence of *T. solium* eggs within the stool of a potential carrier. Whilst this does not necessarily indicate an NCC infection, it does assist in the detection of tapeworm carriers and the consequent disruption of the cycle of transmission. Whilst this method can have high specificity depending on the expertise

Table 1
The 'Del Brutto Criteria' for diagnosis of NCC - adapted from Del Brutto et al. (2001).

Absolute Criteria	Major Criteria	Minor Criteria	Epidemiological Criteria	Diagnosis
Histology: visualisation of parasite from biopsy of brain or spinal cord lesion. Neuroimaging: scolex visible within cystic lesion. Fundoscopy: evidence of sub-retinal parasites.	Neuroimaging: lesions highly suggestive of NCC. EITB assay: positive result for detection of *T. solium* antibodies. Cysticidal drug therapy: lesion resolution following treatment with albendizole or praziquantel.	Neuroimaging: lesions suggestive of NCC. Clinical manifestations: symptoms suggestive of NCC. CSF ELISA: positive detection for detection of *T. solium* antibodies or antigens. Evidence of cysticercosis outside the CNS.	Patient country of origin endemic for NCC. Patient currently resides in NCC endemic area. Patient frequently travels to areas where NCC is endemic. There is evidence that patient household has had contact with *T. solium* infection.	Definitive: 1 absolute OR 2 major plus 1 minor/1 epidemiological. Probable: 1 major plus 2 minor OR 1 major plus 1 minor plus 1 epidemiological OR 3 minor plus 1 epidemiological.

of the examiner, it has very low sensitivity due to a certain threshold of eggs needed to be visible under a microscope (Gilman et al., 2012). Molecular methods applied to stool samples, such as PCR and ELISA, may improve detection rates but like so many other available tests, the equipment and need for trained operators is impractical in many endemic settings (Mahanty and Garcia, 2010). More recently simpler and cheaper methods have been developed for identification of *T. solium* eggs (Nkouawa et al., 2016).

5. Treatment

The heterogeneity of clinical presentations of NCC not only complicates the diagnostic procedure but also affects the management plan for the disease; there can be no single, standard therapeutic approach when so many interconnecting factors must be considered. Before commencing treatment, the complete disease profile must be determined, including evidence of CNS involvement, characterisation of the existing immune response, and the number, location and viability of cysts present. Only once these factors have been ascertained can a treatment plan that is tailored to the individual be determined.

5.1. Cysticidal drugs

The use of cysticidal drugs in the treatment of NCC has attracted controversy, as the use of such drugs may pose more risk to the patient than benefit, due mostly to the extensive inflammatory response that can be stimulated in response to the mass death of cysts within the CNS (Sinha and Sharma, 2009). For this reason, the use of cysticidal drugs is contraindicated in cases that have a pre-existing risk of developing hydrocephalus, such as in sub-arachnoid NCC and encephalitic NCC; in these situations, the inflammation that would occur following treatment may pose a substantial risk of rapidly raising ICP, and even result in death. Therefore, in cases where a definitive diagnosis and characterisation of the infection cannot be provided due to lack of neuroimaging, it is considered unwise to proceed with cysticidal therapy and patients should only be treated with regards to their symptoms (Fogang et al., 2015). Furthermore, it has been suggested that alongside their potential dangers, cysticidal drugs may also be unnecessary, as parenchymal cysts in particular may resolve naturally, following a completely benign and asymptomatic pathway (Garcia et al., 2002). However, several studies have shown that cysticidal drugs do have a positive effect in reducing symptoms such as seizures and headaches, and hasten the resolution of parenchymal lesions; this argument is strengthened by many clinicians' apprehensions over allowing a live parasite to continue its development in the brain without challenge (Sinha and Sharma, 2009; Singhi and Suthar, 2015).

The two most widely accepted cysticidal drugs are albendazole, an imidazole that impairs glucose uptake and metabolism in the parasite, and praziquantel, an isoquinolone that causes parasite paralysis by disrupting calcium pathways and homeostasis (Bobes et al., 2014). These drugs are only applicable in the treatment of viable cysts in the vesicular or early colloidal stages of development, and are ineffective against calcified cysts, as these represent parasites that are already dead (Baird et al., 2013). Albendazole is generally considered to be the drug of choice, with superior efficacy and antiparasitic effect compared to praziquantel, alongside better CSF penetration, less apparent interaction with commonly co-administered drugs such as corticosteroids and a more competitive price (Fogang et al., 2015; Bansal et al., 2014). There remains a lack of clarity surrounding prescription guidelines for these drugs and confusion as to the clinical contexts in which their use is considered appropriate and beneficial.

5.2. Anti-epileptics

Seizures are a commonly reported clinical manifestation of parenchymal NCC. In cases involving evident symptoms and multiple viable cysts, anti-epileptic pharmacological therapy may be indicated (Takayanagui and Odashima, 2006); drugs such as phenobarbitone and carbamazepine are effective in controlling NCC-related seizures in many cases (Del Brutto, 2012). One study found that up to 50% of patients receiving anti-epileptic therapy for NCC suffered relapses in seizure control following drug withdrawal, suggesting that therapy was having an inhibitory effect on seizures stimulated by the presence of cysts (Garcia and Del Brutto, 2005). Again, use of these drugs has attracted controversy, with some studies reporting no improvement in seizure outcome (Fogang et al., 2015).

5.3. Steroids

Administration of steroids is a vital step in the regulation of NCC-related inflammation in the CNS to control the acute inflammatory process that occurs following degradation of viable cysts. Prednisolone or dexamethasone are commonly used as adjuncts to cysticidal therapy and should be administered around 3 days before the cysticidal drugs are administered, then continued for approximately a week following the end of the course (Sinha and Sharma, 2009). In patients with a heavy parasite load and diffuse infection, the use of cysticidal therapy is considered too great a risk and steroids may be used in isolation (Fogang et al., 2015). Concomitant steroid administration has proven to be effective in the prevention of severe inflammatory complications; however, there are still some concerns regarding their use, including the potential for increased parasite survival due to immune suppression and the need for further studies into what constitutes appropriate doses and timing of administration in order to provide optimum benefits (Carpio et al., 2013).

5.4. Surgery

In cases involving extensive infection, such as racemose NCC and severe extra-parenchymal NCC, anticysticidal therapy may not be an option due to risks associated with mass inflammation, but these types of NCC are associated with substantial risk of complications if left untreated. In these cases, a more aggressive approach may be indicated, including cyst extirpation via surgery (Bansal et al., 2014). More commonly, surgery may be advised in severe cases to insert shunts allowing for fluid drainage and resolution of hydrocephalus; shunt dysfunction in these cases is unfortunately relatively common, and associated with increased mortality; simultaneous steroid administration can reduce this risk (Garcia et al., 2002). Surgery was the primary intervention for NCC therapy but with the development of advanced pharmacological therapeutics in this field, the use of surgery has significantly declined, and is now only used in the severest of cases.

6. Future prospects for control and prevention

Control and prevention of *T. solium* transmission should be a key priority in global health as intervention can reduce the substantial healthcare and economic burdens inflicted by both NCC and taeniasis (Torgerson and Macpherson, 2011).

The high biotic potential and environmental stability of tapeworm eggs presents a significant challenge for control but there are a number of simple solutions that could easily be implemented if financial resources were made available to endemic countries. Improved sanitation, increased education within communities to highlight and inform local populations as to the disease and corralling pigs to prevent their contact with human waste are all essential components of any intervention in low and middle income countries (Schantz et al., 1993; Pawlowski, 2016). Increased awareness of infection and transmission is also required in non-endemic developed countries where the disease has shown signs of increasing (Fabiani and Bruschi, 2013; Gilman et al., 2012) and where human carriers of *T. solium* require to be identified and treated on public health grounds (Nkouawa et al., 2016).

One option for prevention and control of NCC is the development of vaccines for application in pigs, of which the TSOL18 vaccine, comprised of a recombinant protein originating from a *T. solium* oncosphere shows promise (Jayashi et al., 2012). The sequencing of the *T. solium* genome also offers exciting prospects in the further improvement of such vaccines through the identification and direct targeting of highly specific antigens (Bobes et al., 2014).

Finally, improved surveillance is needed, including implementing obligatory notification of NCC cases. Accurate assessment of NCC distribution and transmission, is critical to achieving robust disease burden calculations and for targeting of public health interventions. Carpio et al. (2016) provides recommendations for policymakers for a range parasitic diseases affecting the CNS, and if adopted, would provide much needed data that can be used to direct future initiatives. In the absence of reliable estimates of its global burden, NCC will remain – along with other endemic zoonoses of low priority in the eyes of funding agencies (Maudlin et al., 2009; Okello et al., 2015) – a truly neglected disease.

Acknowledgements

This work received financial support from the European Union's Seventh Framework Program (FP7/2007-2013) under grant agreement n° 221948, ICONZ (Integrated Control of Neglected Zoonoses) and THEME [KBBE.2012.1.4-03] under grant agreement n° 312030, Advocacy for the fight against Neglected Zoonotic Diseases (ADVANZ). The contents of this publication are the responsibility of the authors.

References

Baird, R.A., Wiebe, S., Zunt, J.R., Halperin, J.J., Gronseth, G., Roos, K.L., 2013. Evidence-based guideline: treatment of parenchymal neurocysticercosis: report of the guideline development subcommittee of the American Academy of Neurology. Neurology 80, 1424–1429.

Bansal, R., Gupta, M., Bharat, V., Sood, N., Agarwal, M., 2014. Racemose variant of neurocysticercosis: a case report. J. Parasit. Dis, 1–4.

Bobes, R.J., Fragoso, G., Fleury, A., Garcia-Varela, M., Sciutto, E., Larralde, C., Laclette, J.P., 2014. Evolution, molecular epidemiology and perspectives on the research of taeniid parasites with special emphasis on *Taenia solium*. Infect. Genet. Evol. 23, 150–160.

Callacondo, D., Garcia, H.H., Gonzales, I., Escalante, D., Nash, T.E., 2012. High frequency of spinal involvement in patients with basal subarachnoid neurocysticercosis. Neurology 78, 1394–1400.

Carabin, H., Ndimubanzi, P.C., Budke, C.M., Nguyen, H., Qian, Y., Cowan, L.D., Stoner, J.A., Rainwater, E., Dickey, M., 2011. Clinical manifestations associated with neurocysticercosis: a systematic review. PLoS Negl. Trop. Dis. 5, 1–13.

Carpio, A., Romo, M.L., 2014. The relationship between neurocysticercosis and epilepsy: and endless debate. Arq. Neuropsiquiatr. 72, 383–390.

Carpio, A., Fleury, A., Hauser, W.A., 2013. Neurocysticercosis: five new things. Neurol. Clin. Pract. 3, 118–125.

Carpio, A., Romo, M.L., Parkhouse, R.M., Short, B., Dua, T., 2016. Parasitic diseases of the central nervous system: lessons for clinicians and policy makers. Expert Rev. Neurother. 16, 401–414.

Coral-Almeida, M., Gabriel, S., Abatih, E.N., Praet, N., Benitez, W., Dorny, P., 2015. *Taenia solium* human cysticercosis: a systematic review of sero-epidemological data from endemic zones around the world. PLoS Negl. Trop. Dis. 9, 1–20.

Coyle, C.M., Mahanty, S., Zunt, J.R., Wallin, M.T., Cantey, P.T., White, A.C., O'Neal, S.E., Serpa, J.A., Southern, P.M., Wilkins, P., McCarthy, A.E., Higgs, E.S., Nash, T.E., 2012. Neurocysticercosis: neglected but not forgotten. PLoS Negl. Trop. Dis. 6, 1–3.

Crompton, D., Peters, P. (Eds.), 2010. Working to Overcome the Global Impact of Neglected Tropical Diseases: First WHO Report on Neglected Tropical Diseases. World Health Organisation (WHO), 97-103.

Del Brutto, O.H., Sotelo, J., Roman, G.C. (Eds.), 1998. Neurocysticercosis: A Clinical Handbook. Swets and Zeitlinger Publishers, Lisse, pp. 1–7.

Del Brutto, O.H., Rajshekhar, V., White, A.C., Tsang, V.C.W., Nash, T.E., Takayanagui, O.M., Schantz, P.M., Evans, C.A.W., Flisser, A., Correa, D., Botero, D., Allan, J.C., Sarti, E., Gozalez, A.E., Gilman, R.H., Garcia, H.H., 2001. Proposed diagnostic criteria for neurocysticercosis. Neurology 57, 177–183.

Del Brutto, O.H., 2012. Neurocysticercosis: a review. Sci. World J., 1–8.

Fabiani, S., Bruschi, F., 2013. Neurocysticercosis in Europe: still a public health concern not only for imported cases. Acta Trop. 128, 18–26.

Fleury, A., Sastre, P., Sciutto, E., Correia, S., Monedero, A., Toledo, A., Hernandez, M., Harrison, L.J.S., Parkhouse, R.M.E., 2016. A Lateral Flow Assay (LFA) for the rapid detection of extraparenchymal neurocysticercosis using cerebrospinal fluid. Exp. Parasitol. 171, 67–70, http://dx.doi.org/10.1016/j.exppara.2016.10.016.

Fogang, Y.F., Camara, M., Ndiyaye, M.M., 2012. Cerebral neurocysticercosis mimicking or comorbid with episodic migraine? BMC Neurol. 14, 138, http://dx.doi.org/10.1186/1471-2377-14-138.

Fogang, Y.F., Savadogo, A.A., Camara, M., Toffa, D.H., Basse, A., Sow, A.D., Ndiaye, M.M., 2015. Manging neurocysticercosis: challenges and solutions. Int. J. Gen. Med. 8, 333–344.

Gabriel, S., Blocher, J., Dorny, P., Abatih, E.N., Schmutzhard, E., Ombay, M., Mathias, B., Winkler, A.S., 2012. Added value of antigen ELISA in the diagnosis of neurocysticercosis in resource poor settings. PLoS Negl. Trop. Dis. 6, e1851.

Garcia, H.H., Del Brutto, O.H., 2005. Neurocysticercosis: updated concepts about an old disease. Lancet Neurol. 4, 653–661.

Garcia, H.H., Evans, C.A.W., Nash, T.E., Takayanagui, O.M., White, A.C., Botero, D., Rajshekhar, V., Tsang, V.C.W., Schantz, P.M., Allan, J.C., Flisser, A., Correa, D., Sarti, E., Friedland, J.S., Martinez, S.M., Gonzalez, A.E., Gilman, R.H., Del Brutto, O.H., 2002. Current consensus guidelines for treatment of neurocysticercosis. Clin. Microbiol. Rev. 15, 747–756.

Garcia, H.H., Gonzalez, A.E., Rodriguez, S., Tsang, V.C.W., Pretell, E.J., Gonzales, I., Gilman, R.H., 2010. Neurocysticercosis: unravelling the nature of the single cysticercal granuloma. Neurology 75, 654–658.

Gilman, R.H., Gonzalez, A.E., Llanos-Zavalaga, F., Tsang, V.C.W., Garcia, H.H., 2012. Prevention and control of Taenia solium taeniasis/cysticercosis in Peru. Pathog. Glob. Health 106, 312–318.

Ito, A., Budke, C.M., 2014. Culinary delights and travel? A review of zoonotic cestodiases and metacestodiases. Travel Med. Infect. Dis. 12, 582–591.

Ito, A., Nakao, M., Ito, Y., Yuzawa, I., Morishima, H., Kawano, N., Fujii, K., 1999. Neurocysticercosis case with a single cyst in the brain showing dramatic drop in specific antibody titers within 1 year after curative surgical resection. Parasitol. Int. 48 (1), 95–99.

Ito, A., Putra, M.I., Subahar, R., Sato, M.O., Okamoto, M., Sako, Y., Nakao, M., Yamasaki, H., Nakaya, K., Craig, P.S., Margono, S.S., 2002. Dogs as alternative intermediate hosts of Taenia solium in Papua (Irian Jaya), Indonesia confirmed by highly specific ELISA and immunoblot using native and recombinant antigens and mitochondrial DNA analysis. J. Helminthol. 76, 311–314.

Ito, A., Yanagida, T., Nakao, M., 2016. Recent advances and perspectives in molecular epidemiology of Taenia solium cysticercosis. Infect. Genet. Evol. 40, 357–367.
Ito, A., 2015. Basic and applied problems in developmental biology and immunobiology of cestode infections: Hymenlepis, Taenia and Echinococcus. Parasite Immunol. 37, 53–69.
Jayashi, C.M., Gonzalez, A.E., Castillo Neyra, R., Kyngdon, C.T., Gauci, C.G., Lightowlers, M.W., 2012. Characterisation of antibody responses in pigs induced by recombinant oncosphere antigens from Taenia solium. Vaccine 30, 7475–7480.
Jongwutiwes, U., Yanagida, T., Ito, A., Kline, S.E., 2011. Isolated intradural-extramedullary spinal cysticercosis: a case report. J. Travel Med. 18, 284–287.
Kimura-Hayama, E.T., Higuera, J.A., Corona-Cedillo, R., Chavez-Macias, L., Perochena, A., Quiroz-Rojas, L.Y., Rodriguez-Carbajal, J., Criales, J.L., 2010. Neurocysticercosis: radiologic-pathologic correlation. Radiographics 30, 1705–1719.
Kobayashi, K.1, Nakamura-Uchiyama, F., Nishiguchi, T., Isoda, K., Kokubo, Y., Ando, K., Katurahara, M., Sako, Y., Yanagida, T., Ito, A., Iwabuchi, S., Ohnishi, K., 2013. Rare case of disseminated cysticercosis and taeniasis in a Japanese traveler after returning from India. Am. J. Trop. Med. Hyg. 89, 58–62.
Lescano, A.G., Garcia, H.H., Gilman, R.H., Gavidia, C.M., Tsang, V.C.W., Rodriguez, S., Moulton, L.H., Villaran, M.V., Montano, S.M., Gonzalez, A.E., 2009. *Taenia solium* cysticercosis hotspots surrounding tapeworm carriers: clustering on human seroprevalence but not on seizures. PLoS Negl. Trop. Dis. 3, 1–8.
Mahanty, S., Garcia, H.H., 2010. Cysticercosis and neurocysticercosis as pathogens affecting the nervous system. Prog. Neurobiol. 91, 172–184.
Martins-Melo, F.R., Ramos, A.N., Cavalcanti, M.G., Alencar, C.H., Heukelbach, J., 2016. Neurocysticercosis-related mortality in Brazil, 2000–2011: epidemiology of a neglected neurological cause of death. Acta Trop. 153, 128–136.
Maudlin, I., Eisler, M.C., Welburn, S.C., 2009. Neglected and endemic zoonoses. Philos. Trans. R. Soc. Lond. B Biol. Sci. 364, 2777–2787.
Nakao, M., Lavikainen, A., Yanagida, T., Ito, A., 2013. Phylogenetic systematics of the genus Echinococcus (Cestoda: Taeniidae). Int. J. Parasitol. 43, 1017–1029.
Nkouawa, A., Sako, Y., Okamoto, M., Ito, A., 2016. Simple identification of human *Taenia* species by multiplex loop-mediated isothermal amplification in combination with dot enzyme-linked immunosorbent assay. Am. J. Trop. Med. Hyg. 94, 1318–1323.
Okello, A.L., Beange, I., Shaw, A., Moriyón, I., Bardosh, K., Gabriel, S., Saarnak, C., Vang Johanssen, M., Mukaratirwa, S., Berkvens, D., Welburn, S.C., 2015. Raising the political profile of the neglected zoonotic diseases: three complementary European commission-funded projects to streamline research, build capacity and advocate for control. PLoS Negl. Trop. Dis. 9 (3), e0003505.
Pawlowski, Z., 2016. Taeniosis/neurocysticercosis control as a medical problem—a discussion Paper. World J. Neurosci. 6, 165–170.
Sako, Y., Takayanagui, O.M., Odashima, N.S., Ito, A., 2015. Comparative study of paired serum and cerebrospinal fluid samples from neurocycisticercosis patients for the detection of specific antibody to *Taenia solium* immunodiagnostic antigen. Trop. Med. Health 43 (3), 171–176.
Schantz, P.M., Cruz, M., Sarti, E., Pawlowski, Z., 1993. Potential eradicability of taeniasis and cysticercosis. Bull. Pan Am. Health Organiz. 27, 397–403.
Singhi, P., Suthar, R., 2015. Neurocysticercosis. Indian J. Paediatr. 82, 166–171.
Sinha, S., Sharma, B.S., 2009. Neurocysticercosis: a review of current status and management. J. Clin. Neurosci. 16, 867–876.
Sorvillo, F., Wilkins, P., Shafir, S., Eberhard, M., 2011. Public health implications of cysticercosis acquired in the United States. Emerg. Infect. Dis. 17, 1–6.
Takayanagui, O.M., Odashima, N.S., 2006. Clinical aspects of neurocysticercosis. Parasitol. Int. 55, 111–115.
Torgerson, P.R., Macpherson, C.N., 2011. The socioeconomic burden of parasitic zoonoses: global trends. Vet. Parasitol. 182, 79–95.
Tuero, I., Palma, S., Cabeza, F., Saleemi, S., Rodriguez, S., Gonzales, I., Mayta, H., Mahanty, S., Garcia, H.H., Gilman, R.H., 2015. A comparative study of peripheral immune responses to *Taenia solium* in individuals with parenchymal and subarachnoid neurocysticercosis. PLoS Negl. Trop. Dis. 9, 1–15.
WHO: Taeniasis/cysticercosis. URL: http://www.who.int/mediacentre/factsheets/fs376/en/. (Accessed 25 August 2016).
Yanagida, T., Yuzawa, I., Joshi, D.D., Sako, Y., Nakao, M., Nakaya, K., Kawano, N., Oka, H., Fujii, K., Ito, A., 2010. Neurocysticercosis: assessing where the infection was acquired from. J. Travel Med. 17, 206–208.
Yanagida, T., Carod, J.-F., Sako, Y., Nakao, M., Hoberg, E.P., Ito, A., 2014. Genetics of the pig tapeworm in Madagascar reveal a history of human dispersal and colonization. PLoS One 9, e109002.