Neurocysticercosis infection and disease—A review

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A B S T R A C T

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.

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0001-706X/© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 inter-connecting 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 (Takayanagi 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 scolexes to evacuate 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 Buschi, 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 Buschi, 2013).

Areas endemic for NCC include Latin America, Africa, South East Asia, India, China and Nepal (Fabiani and Buschi, 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 (Tuoer 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 (Tuoer 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 sur-
rounding nerves leading to entrainment 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 subarach-
noid 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 vari-
sious 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 tran-
sient 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 resul-
t, cysts originating in the basal cisterns may follow a gravity-depen-
dent 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 diag-
nostic criteria in an attempt to combine aspects of clinical history,
neuroimaging and immunological evidence, as well as epidemi-
ological 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
circumstances.

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 den-
sity 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
’sizzly 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 sensi-
tivity for detection of calcifications that occur in approximately 50%
of patients (Singhi and Sharma, 2009). The higher resolution of MRI
scans, permit better distinction of the degenerative stage of cys-
ticerci 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 immuno-
electrotransfer 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 signif-
ically 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 infec-
tion 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. Gab-
riel 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 infec-
tion (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
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).

### Table 1

The ‘Del Brutto Criteria’ for diagnosis of NCC - adapted from Del Brutto et al. (2001).

<table>
<thead>
<tr>
<th>Absolute Criteria</th>
<th>Major Criteria</th>
<th>Minor Criteria</th>
<th>Epidemiological Criteria</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology:</td>
<td>Neuroimaging:</td>
<td>Neuroimaging:</td>
<td>Patient country of origin</td>
<td>Definitive:</td>
</tr>
<tr>
<td>visualisation of</td>
<td>lesions highly suggestive of</td>
<td>lesions suggestive of NCC.</td>
<td>endemic for NCC</td>
<td>1 absolute</td>
</tr>
<tr>
<td>parasite from</td>
<td>NCC, EITB assay:</td>
<td>Clinical manifestations:</td>
<td>Patient currently resides in</td>
<td>OR 2 major plus 1 minor/1</td>
</tr>
<tr>
<td>biopsy of brain or</td>
<td>positive result for detection of</td>
<td>symptoms suggestive of NCC.</td>
<td>NCC endemic area.</td>
<td>1 epidemiological.</td>
</tr>
<tr>
<td>spinal cord</td>
<td><em>T. solium</em> antibodies.</td>
<td>CSF ELISA:</td>
<td>Patient frequently travels to</td>
<td>Probable:</td>
</tr>
<tr>
<td>lesion.</td>
<td>Cysticidal drug therapy:</td>
<td>positive detection for</td>
<td>areas where NCC is endemic.</td>
<td>1 major plus 2 minor</td>
</tr>
<tr>
<td>Neuroimaging:</td>
<td>lesions resolution following treatment</td>
<td><em>T. solium</em> antibodies or</td>
<td>There is evidence that patient</td>
<td>OR 1 major plus 1 minor plus 1</td>
</tr>
<tr>
<td>scolose visible within cystic</td>
<td>with albendazole or</td>
<td>antigens.</td>
<td>household has had contact</td>
<td>1 epidemiological</td>
</tr>
<tr>
<td>lesion.</td>
<td>praziquantel.</td>
<td>Evidence of cysticercosis</td>
<td>with <em>T. solium</em> infection.</td>
<td>OR 3 minor plus 1 epidemiological.</td>
</tr>
<tr>
<td>Fundoscopy:</td>
<td></td>
<td>outside the CNS.</td>
<td></td>
<td></td>
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<tr>
<td>evidence of sub-retinal</td>
<td></td>
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<td>parasites.</td>
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</tbody>
</table>
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 TSO1L18 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.

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