Landscape analysis: management of neurocysticercosis with an emphasis on low- and middle-income countries

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Contents

A. Literature selection

A literature search was conducted using the following search engines: PubMed, PubMed Central, Cochrane, Embase, GoogleScholar, Medline and ScienceDirect. Papers were mainly collected from PubMed using the following search terms and combinations thereof: “treatment”, “management”, “neurocysticercosis”, “resource-poor”, “Asia”, “Africa”, “South America”, “Latin America”, “HIV/AIDS”, “spinal”. Cross-linked literature was screened and added, where appropriate. No time restrictions concerning the year of publication limited the literature search.

Primary selection of English language citations was conducted according to title and abstracts. In a second step eligible full articles or electronic publications were assessed for sought topics. Duplicates were removed (on title, author, year, journal, DOI). Moreover, clinical notes, letters to the editor and PubMed comments were initially included in the search procedure. Selection of citations for the landscape analysis was tailored to acquisition of data from or about low- and middle-income countries (LMIC). If this criterion was met, no geographical limitation was applied.

Background information on *Taenia solium* (neuro)cysticercosis was retrieved from the WHO/FAO/OIE Guidelines for the surveillance, prevention and control of taeniosis/cysticercosis (Murrell et al. 2005) and a book chapter on neurocysticercosis in sub-Saharan Africa (Winkler 2013) as well as selected recent reviews on NCC (Winkler et al. 2009a, Nash & Garcia 2011, Garcia et al. 2011a, Takayanagui et al. 2011, Winkler 2012, Garcia et al. 2014a).

Moreover, literature collections by AS Winkler were screened and added, if appropriate, to supplement data predominantly for sub-Saharan Africa.

Articles were excluded, if they

- did not relate to humans
- did not relate to LMIC, or highly endemic areas
- did not discuss issues relevant to diagnosis, management and control of T. solium (neuro)cysticercosis

A chart illustrating the search and exclusion process is presented in figure 1.

B. Prevalence of neurocysticercosis in low- and middle-income countries

Neurocysticercosis (NCC) represents the most common helminthic infection of the central nervous system (Del Brutto 2006) and is endemic in most countries of Latin America, Asia and sub-Saharan Africa.

1. Seroprevalence of *Taenia solium* cysticercosis in Latin America, Asia and sub-Saharan Africa

Community-based estimation of the prevalence of NCC is difficult as neuroimaging would have to be applied to a large population putting seemingly healthy people at risk of radiation, and therefore has been performed rarely so far (Fleury et al. 2003). In contrast, the prevalence of human *T. solium* cysticercosis in communities has been assessed, as this requires blood analysis only.

In Latin America, including Mexico, Peru, Ecuador, Guatemala and Bolivia the prevalence of *T. solium* cysticercosis as measured by antibody-ELISA and/or western blot was 3.7-12.2%, 5-24%, 10.4%, 10-17% and 22.4%, respectively (Flisser et al. 2003, Murrell 2005, Flisser & Gyorkos 2007, Flisser 2013).

In Asia, seroprevalence data are scarce, but reports are slowly emerging showing that *T. solium* cysticercosis presents a non-negligible public health problem. Most Asian studies demonstrate high seroprevalence rates using mainly antibody-ELISA and/or western blot (Rajshekhar et al. 2003). Indonesia is the best examined country when it comes to community-based data with seroprevalence rates of 2-13%, but has also shown estimates of as high as 50% in Irian Jaya (Simanjuntak et al. 1997, Subahar et al. 2001). Reports from China demonstrate prevalence rates of 2-6%, which may climb to 11% in some provinces. It was estimated that around three million people with cysticercosis live in China (Rajshekhar et al. 2003, Li et al. 2006).

In sub-Saharan Africa, community-based seroprevalence data on *T. solium* cysticercosis are emerging. In cysticercosis endemic areas of the Democratic Republic of Congo, Tanzania, Burkina Faso and Zambia the seroprevalence rates of *T. solium* cysticercosis as measured with an antigen-ELISA were 22%, 17%, 10% and 5.8%, respectively (Carabin et al. 2009, Kanobana et al. 2011, Mwape et al. 2012, Mwanjali et al. 2013).

2. Prevalence of neurocysticercosis in Latin America, Asia and sub-Saharan Africa

Reports on autopsy results mainly come from Latin America and show NCC in 5.9%, 2.8% and 2.4% of the examined cases in Peru, Mexico and Brazil, respectively (Murrell 2005). As autopsy results are not routinely available indirect hospital- or community-based approaches are used to get an impression about the prevalence of people with NCC in certain populations and often people suffering from epileptic seizures/epilepsy (PWE) or

other neurological disorders are included into these studies. Description of hospital-based NCC cases mainly through examination of PWE are numerous in Latin America and India and will not be reported here, instead the analysis will focus on community-based studies which are more representative.

A recent meta-analysis of epilepsy and NCC in Latin America revealed a median NCC proportion among PWE of 32.3% (Bruno et al. 2013). Community-based studies from Honduras, Peru, Bolivia and Ecuador determining the prevalence of NCC among people with active epilepsy based on serology and computed tomography (CT) showed the following results: Honduras 36.6% (Medina et al. 2005), Peru 35.1% (Moyano et al. 2014), Ecuador 33% (Del Brutto et al. 2005) and Bolivia 27.4% (Nicoletti et al. 2005). In a previous study from Peru, 54% of people with active epilepsy and 14% of individuals without seizures undergoing CT had NCC (Cruz et al. 1999). Another Peruvian study looked at CT-based NCC prevalence in PWE (active and inactive), which yielded 38.5%, and in people without epilepsy subdivided in those with positive and negative serology, showing 34% and 13.8%, respectively (Montano et al. 2005). A study from Guatemala that included PWE (not specified whether active or inactive) and people without epilepsy showed a CT-based NCC prevalence of 47% and 24%, respectively (Garcia-Noval et al. 1996). A study from Mexico that was designed to determine the seroprevalence rates of cysticercosis and taeniosis found 70% of people (7/10) with a history of seizures to have NCC lesions on CT scan (Schantz et al. 1994). The calculation of a morbidity estimate for Latin America yielded approximately 400 000 people suffering from symptomatic NCC (Bern et al. 1999).

In China (Sichuan Province), PWE (not specified whether active or inactive) within a community-based study that was designed to assess the prevalence of *T. solium* taeniosis/cysticercosis had a significantly higher *T. solium* cysticercosis seroprevalence (16.4%) compared to those without epilepsy (2.5%; Li et al. 2006). A study that was conducted in a south Indian community recruited people with active epilepsy and found that 34% had NCC based on CT and serology (Rajshekhar et al. 2006).

In sub-Saharan Africa prevalence rates of NCC in PWE are mainly based on serological results and are contributed from a few countries only with results of over 40% (Cameroon) and over 50% (Burundi), depending on the serological tests and the methodological approaches used (Mafojane et al. 2003, Nsengiyumva et al. 2003, Zoli et al. 2003a,b, Winkler et al. 2009a). High seroprevalence rates of NCC in PWE of whom a selected amount was confirmed with neuroimaging has also been reported from Burkina Faso and Rwanda (Millogo et al. 2012, Rottbeck et al 2013). A recent meta-analysis that only included African studies showed a significant association between epilepsy and cysticercosis with an odds ratio of 3.4 (Quet et al. 2010). More details on the prevalence of NCC (serology and neuroimaging) are available from South African studies (Mafojane et al. 2003), where one study found 50.6% of newly diagnosed PWE showing lesions of NCC on neuroimaging (Campbell et al. 1987). One neuroimaging based study in sub-Saharan Africa outside South Africa demonstrated definite NCC lesions on CT in 2.4% of PWE, lesions highly suggestive of NCC were present in 11.3% and lesions compatible with NCC were seen in 4.2%. The NCC lesions were significantly more common in PWE compared to the controls (Winkler et al. 2009c). Unpublished CT data from

over 1000 PWE from *T. solium* (neuro)cysticercosis endemic areas of three African countries (Tanzania, Uganda, Malawi) indicate prevalence rates from 2-3% in urban areas and from over 10% in rural areas (unpublished data AS Winkler). The highest prevalence rate of CT confirmed NCC in PWE of over 50% outside South Africa comes from a study in Zambia (personal communication J Blocher and S Gabriel).

The total of all people suffering from NCC, including symptomatic and asymptomatic cases, would be estimated somewhere between 2.56-8.30 million (Winkler 2013) based on the range of epilepsy prevalence data available, which is between 4-13/1000 for sub-Saharan Africa (Edwards et al. 2008, Winkler et al. 2009b), and the contribution of NCC to epilepsy in approximately 30% of cases (Ndimubanzi et al. 2010). To that number people with other neurological symptoms/signs due to NCC and those asymptomatic have been added (for more details refer to Winkler 2013). These figures would however come down if only areas confirmed with endemic *T. solium* (neuro)cysticercosis would be considered. Currently a population of NCC based epilepsy of 0.76-2.46 million and a population of symptomatic NCC of 0.95-3.08 million are estimated for sub-Saharan Africa (Winkler 2013). The latter numbers also include people with other neurological disorders resulting from NCC such as headaches, whereby the occurrence of headaches seems to be underestimated in NCC related symptoms/signs (personal experience AS Winkler), which suggests that the actual number of people suffering from symptomatic NCC may even be higher. Interestingly, a high proportion (18.4%) of psychiatric inpatients showed results attributable to NCC on western blotting in a Venezuelan community (Meza et al. 2005). Prevalence rates of 144/1000 were reported in rural settings in Ecuador (Cruz et al. 1999). The prevalence of NCC in patients with psychiatric disorders so far has not been explored on the African continent and may further increase total numbers of those suffering from symptomatic NCC. The same amount of people suffering from symptomatic NCC would also suffer from asymptomatic NCC, if assuming that 50% of all cases do not display symptoms. Latent NCC cases when harbouring *T. solium* cysticerci can become symptomatic at any time due to the natural course of disease or in the context of mass treatment received for different intestinal parasites (Ramos-Zuniga et al. 2013) or soil-transmitted helminths and schistosomiasis (Winkler 2013).

3. Prevalence of neurocysticercosis in special populations

A trend of higher ages in subjects with both epilepsy and NCC and late seizure onset as compared to other aetiologies was reported (Blocher et al. 2011). This has also been observed in endemic settings on the South American continent (Medina et al. 1990, Rigatti et al. 1999, Del Brutto et al. 2005, Nicoletti et al. 2005). However, some studies from Latin America, Asia and sub-Saharan Africa clearly demonstrate NCC in children and adolescents and therefore these age groups have to be considered when it comes to the planning of community-based studies. In addition, one also needs to be aware of the presence of NCC in children in the context of the potentially hazardous mass drug administration with albendazole and/or praziquantel for other helminthic parasites and the evaluation of differential diagnoses in childhood epilepsy (Cruz et al. 1999, Montano et al. 2005, Li et al. 2006, Nkouawa et al. 2010a). An interesting phenomenon is also the increasing prevalence

in Muslim countries previously not endemic to NCC. This may be due to increased international travel or immigrants from pork eating countries that are asymptomatic *T. solium* carriers with the potential of causing autochthonous cases of NCC without the need for infected pigs (Khan et al. 2011, Del Brutto 2013, Farahani et al. 2013).