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Mini review on chemotherapy of taeniasis and cysticercosis due to Taenia solium in Asia, and a case report with 20 tapeworms in China.

Ito A, Li T, Chen X, Long C, Yanagida T, Nakao M, Sako Y, Okamoto M, Wu Y, Raoul F, Giraudoux P, Craig PS.

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Review Paper

Mini review on chemotherapy of taeniasis and cysticercosis due to *Taenia solium* in Asia, and a case report with 20 tapeworms in China

Ito, A.[1*], Li, T.[2], Chen, X.[2], Long, C.[3], Yanagida, T.[1], Nakao, M.[1], Sako, Y.[1], Okamoto, M.[4], Wu, Y.[5], Raoul, F.[6], Giraudoux, P.[6,7] and Craig, P.S.[8]
[1]Asahikawa Medical University, Asahikawa, Hokkaido, Japan
[2]Institute of Parasitic Diseases, Sichuan Centers for Disease Control and Prevention, Chengdu, Sichuan, China
[3]Yajiang County Centers for Disease Control and Prevention, Yajiang, Ganzi Tibetan Prefecture, Sichuan, China
[4]Primate Research Institute, Kyoto University, Inuyama, Aichi, Japan
[5]College of Veterinary Medicine, Sichuan Agricultural University, Chengdu, Sichuan, China
[6]University of Franche-Comté/CNRS, Besançon, France
[7]Institut Universitaire de France, Paris, France
[8]School of Environment and Life Sciences, University of Salford, UK
[*]Corresponding author email: akiraito@asahikawa-med.ac.jp
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Abstract. A 43-year-old Tibetan woman living in northwest Sichuan, China, confirmed to be a taeniasis carrier of *Taenia solium* was treated with pumpkin seeds combined with Areca nut extract in October 2009. All 20 tapeworms except one without scolex were expelled under good conditions. She was free of secondary cysticercosis within one year follow up. Although the first choice for treatment of taeniasis is still praziquantel, it may often cause serious side effect on asymptomatic cysticercosis cases to suddenly become symptomatic within a half day of the treatment. Therefore, the problems in treatment of taeniasis and/or cysticercosis in Asia are briefly overviewed, since other platyhelminthic diseases including schistosomiasis, opisthorchiasis etc. are more common and praziquantel is strongly recommended for mass treatment of these trematodiases with no idea on the co-infection with eggs of *T. solium* which cause asymptomatic cysticercosis.

INTRODUCTION

Cysticercosis due to the metacestode(s) of *Taenia solium* is one of the most serious parasitic infections spreading almost all over the world, and listed as one of the WHO Neglected Tropical Diseases (NTDs) or Neglected Zoonotic Diseases (NZDs) (Craig *et al*., 2007; Flisser *et al*., 2011; WHO, 2011). As the intermediate host of this parasite is mainly swine, cysticercosis is common in developing countries where people eat raw or undercooked pork due to poor meat inspection (Schantz *et al*., 1993, 1998; Allan *et al*., 1996; Craig *et al*., 1996; Simanjuntak *et al*., 1997; White, 1997; Singh *et al*., 2002; Ito *et al*., 2003a, 2004; Wandra *et al*., 2003, 2011; Chen *et al*. 2005; Li *et al*., 2006; Anantaphruti *et al*., 2007). However, through globalization, it is no more local disease in rural or remote areas in developing countries but also emerging disease in developed countries. Recent trends in international tourism into remote or rural areas, expansion of global

business and the increase in the number of transmigrants from rural to urban areas, immigrants and refugees have drastically increased the risk of cysticercosis in developed countries (Croker *et al.*, 2010; Yanagida *et al.*, 2010, 2012; Jongwietiwes *et al.*, 2011; Serpa *et al.*, 2011; Sorvillo *et al.*, 2011; Del Brutto, 2012; Del Brutto & Garcia, 2012), orthodox Jewish (Schantz *et al.*, 1992; Leshem *et al.*, 2011) and Muslim communities (Margono *et al.*, 2006; Hira *et al.*, 2004).

In remote and/or rural areas in China, cysticercosis is still common (Yingkun *et al.*, 1979; Ito *et al.*, 2003b; Chen *et al.*, 2005; Ikejima *et al.*, 2006; Li *et al.*, 2006). In a population screening program for taeniasis/cysticercosis performed in a Tibetan community of northwest Sichuan, we have confirmed that *T. solium*, *Taenia saginata* and *Taenia asiatica* were co-endemic (Li *et al.*, 2006), and that one woman expelled 20 tapeworms of *T. solium* after treatment with Chinese medicine. As such a massive infection of *T. solium* with intact scoleces is very rare, we report this case and stress the usefulness of pumpkin seeds combined with Areca nut extract (Li *et al.*, 2012) and the problems caused by the use of praziquantel.

A CASE REPORT WITH 20 TAPEOWRMS OF *T. SOLIUM* AND THE BACKGROUND INFORMATION

Questionnaire investigations in October 2009 in Yajiang, Sichuan, China, revealed that both a 43 years old woman and her 16-years-old son, who had no detectable health problem or abdominal symptoms, had *Taenia* tapeworms. They observed expulsion of proglottids in faeces only once, one and two months before, respectively. Following treatment with traditional Chinese medicine (Li *et al.*, 2012), 20 mature tapeworms of approximately 1 m long each were recovered from the woman. Maturity of the tapeworms was confirmed not only by microscopic observation of fully developed eggs but also by successful experimental infection of pigs using the gravid proglottids (data not shown). All except one were intact with scoleces (Figure 1A) with two rows of hooklets (Figure 1B) and were morphologically identified as *T. solium*. Each worm was further confirmed to be the Chinese haplotype in the Asian genotype of *T. solium* by haplotype analysis and multiplex PCR (data not shown) (Yamasaki *et al.*, 2004).

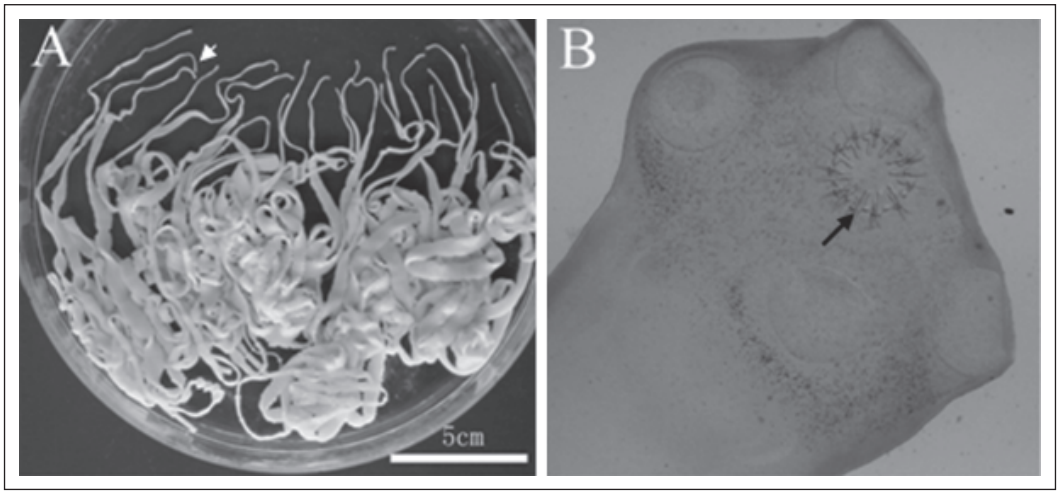

Figure 1. Twenty *Taenia solium* tapeworms expelled from a 43-year-old Tibetan woman following treatment with the Chinese medicine. (A) Macromorphology of twenty tapeworms: Scoleces in round shape were observed in 20 worms except one (the white arrow indicated). (B) Morphology of the scolex of an intact worm under microscope (x40): The scolex was characterized by two rows of hooklets (the black arrow referred) on the rostellum besides four suckers

We failed in confirming of worms from her son during our short stay in the village, since he absconded from the local clinic during the treatment and expelled tapeworms elsewhere but did not bring them back to us. Nevertheless, DNA products specific for Asian genotype of *T. solium* were successfully amplified from his fecal sample by copro-PCR (data not shown)(Yamasaki *et al.*, 2004; Yanagida *et al.*, 2010).

For the case presented here, it would be important to know whether taeniasis carriers suffered from secondary cysticercosis or not. Serology for the detection of specific antibodies in ELISA for *T. solium* cysticercosis using highly reliable recombinant chimeric antigens (Sako *et al.*, 2000; Sato *et al.*, 2003, 2006) was negative in both the mother and the son, suggesting that they were free of secondary cysticercosis. The mother was followed up one year later: she gained in weight, and no more proglottids were found in her faeces. Copro-PCR test became negative and indicated cured of *T. solium* taeniasis. Serology remained negative. However, we have to follow up these two carriers serologically for one or two more years.

The economic status of this family was extremely poor, primarily due to the fact that her husband suffered from lung tuberculosis for many years and passed away in 2010. In January 2009, a pig was slaughtered at home for celebration of Chinese New Year. Although family members recognized the pork full of cysticerci, all of them ate the meat. Therefore, we expected that all the family members should have acquired tapeworms of *T. solium*.

GENERAL ASPECTS OF TAENIASIS/ CYSTICERCOSIS (T/C) IN ASIA

It is common knowledge that *Taenia solium* Linnaeus, 1758 was named by Linné on the belief that it was found solitary in human small intestine, and multiple tapeworm infections even with two worms of *T. solium* were not common. During our field survey from 2005 onwards in Sichuan, China, however, multiple tapeworm infections with *T. solium*, *T. saginata* or *T. asiatica* or mixed worms of these species were not so rare (Li *et al.*, 2006, unpublished data). Similar situations have been found in Thailand (Anantaphruti *et al.*, 2007, 2010) and Indonesia (Simanjuntak *et al.*, 1997).

The high risk of cysticercosis due to *T. solium* is the tapeworm carriers themselves. Furthermore, household contacts are more likely to cause high rates of cysticercosis in tapeworm carriers and their family members. As a consequence, secondary cysticercosis, especially disseminated cysticercosis is expected to be much more frequent in such a context (Yingkun *et al.*, 1979; Schantz *et al.*, 1998; Garcia *et al.*, 1999; Gilman *et al.*, 2000; Chen *et al.*, 2005; Yanagida *et al.*, 2012; Kobayashi *et al.*, 2013).

CHEMOTHERAPY OF TAENIASIS AND CYSTICERCOSIS (T/C)

The drug recommended for treatment of T/C is praziquantel (PZQ). It causes serious damage to the adult worms in the intestine or cysticerci in the parenteral tissues (Pawlowsiki, 2006).

Praziquantel (PZQ) vs Niclosamide

Praziquantel destroys and purges the tapeworms from the intestine and simultaneously damages the cysticerci in parenteral tissues including the brain and causes sudden outcome of seizure attack or convulsion etc., acute symptomatic NCC within a half day of the treatment (Flisser *et al.*, 1993; Sarti *et al.*, 1994; Wandra *et al.*, 2011). We have some experience for taeniasis carriers due to *T. saginata* to be admitted to hospitals within a half day of treatment with PZQ in Bali, Indonesia (Wandra *et al.*, 2003, 2011; Sudewi *et al.*, 2008). Although we investigated to detect taeniasis carriers due to *T. solium* in communities in Bali where cysticercosis was historically common at least two-three decades ago (Theis *et al.*, 1994; Sutisna *et al.*, 1999), we exclusively detected more than 100 taeniasis carriers exclusively due to *T. saginata* from 2002

until 2010 (Wandra *et al.*, 2011). Nonetheless, we confirmed sporadic symptomatic NCC cases in the hospital of University of Udayana, Denpasar, and faced unexpected NCC cases just after the treatment with PZQ of taeniasis carriers due to *T. saginata* in the communities (Sudewi *et al.*, 2008). So, it is evident that both *T. saginata* and *T. solium* are endemic in Bali, even though the latter is now rare or difficult to be confirmed (Swastika *et al.*, 2012).

So, such dual infection of 1) adult tapeworms of *T. saginata* or *T. asiatica* and *T. solium* (Li *et al.*, 2006; Ananthaphruti *et al.*, 2007) and 2) tapeworms of *T. saginata* or *T. asiatica* and cysticerci of *T. solium* may not be rare in remote or rural areas in Southeast Asian countries where people eat uncooked pork and beef under poor meat inspections (Coker-Vann *et al.*, 1981; Singh *et al.*, 2002; Ito *et al.*, 2003a; Ikejima *et al.*, 2005; Li *et al.*, 2006; Wandra *et al.*, 2006, 2011; Anantaphruti *et al.*, 2007).

Due to the severe side effect of PZQ mentioned above, albendazole has strongly been recommended as an alternative drug for either symptomatic or asymptomatic NCC (St Geme *et al.*, 1993; Garcia *et al.*, 2002; Pawlowski, 2006; Sotelo, 2011; Takayanagui *et al.*, 2011).

In the majority of Asian countries where we have many different food-borne trematodiases (FBTs) and/or schistosomiasis, PZQ has widely and strongly been recommended for the treatment, especially for mass treatment. However, there is no data on the people, who are confirmed to have suffered from those trematodiases, are free of *T. solium* taeniasis and/or cysticercosis. So, it is easy to expect that sudden death or sudden seizure attack or convulsion at least just after treatment with PZQ might be not so rare in such remote or rural areas where schistosomiasis and/or FBTs are endemic but there is no hospital or health center for the treatment of cysticercosis (Soukhathammavong *et al.*, 2011; Lovis *et al.*, 2012). Therefore, we strongly recommend 1) not to use PZQ for treatment of taeniasis carriers in the communities where *T. solium* may be co-distributed, or 2) to use PZQ with steroid for taeniasis carriers who are admitted to the hospital to prevent unexpected seizure attack as reported in Mexico (Flisser *et al.*, 1993; Sarti *et al.*, 1994). However, the latter 2) is not feasible in rural and remote areas in Asia where there is no hospital or even health center. Furthermore, we have to be cautious of sudden death or seizure attack occurring after treatment with PZQ for local people who are suffering from those trematodiases in Asian countries (Soukhathammavong *et al.*, 2011; Lovis *et al.*, 2012), and to follow up if they are co-infected with *T. solium*, either with adult worms and/or metacestodes.

We really need to apply highly reliable tools for detection and identification of taeniasis carriers and cysticercosis in humans and pigs (Ito, 2002; Ito & Craig, 2003; Ito *et al.*, 2006). We have to keep in mind that we are living in the environment where we have many parasitic diseases other than the targeted diseases which were screened for some special purposes, schistosomiasis or FBTs such as opisthorchiasis, clonorchiasis, fascioliasis, paragonimiasis etc. in Asia (Soukhathammavong *et al.*, 2011; Lovis *et al.*, 2012). Such a situation may not be always unique to Asia but also cosmopolitan. We should not ignore this real situation of NTDs especially in remote or rural areas in developing countries. So, we are using niclosamide for the treatment of taeniasis in Indonesia (Wandra *et al.*, 2006, 2011), especially after we faced unexpected seizure attacks just after treatment with PZQ (Wandra *et al.*, 2011), and in Thailand (Anantaphruti *et al.*, 2007).

Although NCC is suspected in developing countries where the late onset epilepsy is recorded and *T. solium* is confirmed to be distributed (Ito *et al.*, 2006), children younger than 15 years old may often have history of epileptic attacks even in Africa (Nkouawa *et al.*, 2010). Therefore, we have to screen people in the targeted areas or villages and collect data if there are any people who have history of epilepsy and analyze using highly reliable serological tools in order to confirm if NCC cases are present or not (Theis *et al.*, 1994; Ikejima *et al.*, 2005; Ito *et al.*, 2006;

Nkouawa *et al.*, 2010). This should be the minimum task for people who are working for control of schstosomiasis and FBTs in Asia.

Pumpkin seeds combined with Areca nut extract

Although the ingestion of pumpkin seeds combined with Areca nut extract are rather well known to be effective for treatment of tapeworm carriers as a traditional Chinese medicine, we have not much detailed information on the effect of the pumpkin seed (Pawlowski & Schultz, 1972). Most recent work using pumpkin seeds combined with Areca nut extract revealed that they were highly effective and much better and safer especially for treatment of taeniasis due to *T. solium* (Li *et al.*, 2012) as shown in this case report. Arecoline is one of the components of the Areca nut (*Areca catechu*) (Cox *et al.*, 2010). Based on our experience in treatment of taeniasis carriers, either *T. solium* or *T. saginata* or *T. asiatica*, the combination of pumpkin seeds and Areca nut extract is the safest drug, especially in a context where *T. solium* is present and there is high risk of cysticercosis (Yingkun *et al.*, 1979; Li *et al.*, 2006; Chen *et al.*, 2012).

FUTURE CONTROL OF TAENIASIS AND CYSTICERCOSIS IN ASIA

Taeniasis and cysticercosis due to *T. solium* is neglected in almost all Asian countries including Muslim communities including Malaysia (Noor Azian *et al.*, 2006) and Indonesia (Margono *et al.*, 2006; Wandra *et al.*, 2011). Through our international joint projects on cestode zoonoses in Asia from 1994, we detected indigenous T/C cases due to *T. solium* from almost all countries in Asia: Korea, China, Taiwan, the Philippines, Vietnam, Cambodia, Lao PD, Thailand, Malaysia, Indonesia, Papua New Guinea, Nepal and India (Coker-Vann *et al.*, 1981; Simanjuntak *et al.*, 1997; Singh *et al.*, 2002; Ito *et al.*, 2003a). We have no doubt that Myanmar is also highly endemic (Coker-Vann *et al.*, 1981), since many refugees from Myanmar to Thailand are taeniasis carriers of *T. solium* (Anantaphruti *et al.*, 2007, 2010; Kusolsk *et al.*, unpublished). By contrast, all T/C cases in Japan were imported cases (Yanagida *et al.*, 2012).

What should Japanese experts or JICA (Japan International Cooperation Agency) contribute for future sustainable cooperation for eradication of these NTDs?

Sustainable education of people, especially for school kids as we, Japanese used to do for eradication of parasitic diseases in Japan (Kobayashi *et al.*, 2006; Kojima & Takeuchi, 2006), is recommended for future eradication of NTDs including T/C and echinococcosis (not discussed in this issue) (Ito *et al.*, 2003b; Craig *et al.*, 2007; WHO, 2011) as well as soil transmitted helminhthiases (STHs) and FBTs and schistosomiasis in Asia. Japan is the only country where we have eradicated almost all NTDs including schistosomiasis, clonorchiasis etc. as well as STHs. So, scientific and technical contribution of Japanese experts on FBTs was enormous. Japanese societies of Infectious Diseases or Parasitology or Tropical Medicine or Public Health have to evaluate the Japanese experts' contribution not only on STHs but other FBTs and schistosomiasis. Through Hashimoto Initiative (Kojima & Takeuchi, 2006) at the G8 countries' summit at Denver in 1997 and Birmingham in 1998, Japanese Government declared to support eradication or control of NTDs. But, the target diseases were mainly STHs and malaria, and less schistosomiasis, filariasis, trypanosomiasis, leishmaniasis through bilateral economic cooperative projects in Asia and in Africa as Official Development Assistance (ODA). On 10 November 2012, Hashimoto Initiative Memorial Symposium for Neglected Tropical Diseases was held in Tokyo. The main discussion was evaluation of the historical Japanese contribution for control of NTDs in Asia and in Africa through this Initiative with reasonably high success and impacts. However, there was almost no message for sustainable future contribution from Japan even though many foreign experts including

WHO, World Bank etc. pointed it out. We, therefore, are right now facing how to keep or reconstruct sustainable Japanese contribution for eradication of NTDs in the future.

As NTDs have never got high priority through governmental economic cooperation or business with the counterparts, the Japanese Government including JICA, therefore, better prepare a list of experts for the 17 NTDs in Japan and what kind of tools or technologies are sustainably provided by these experts or by ODA projects from Japan, and show the list with the information to all developing countries. NTDs in each developing country may highly differ. For example, the top NTD in Mongolia is enterobiasis and the second is cystic echinococcosis but never the common STHs such as ascariasis or hookworm infections. The governments of developing countries have no information on the successful experience or advanced tools developed or established for eradication of these NTDs in Japan. It is the reason why we strongly recommend the Japanese Government to prepare such a list of experts against the 17 NTDs and provide the list to the counterpart Governments of developing countries. Without such information on NTDs from Japan or other developed countries, it is impossible for the Governments of developing countries to keep NTDs with some priorities at all, since NTDs are completely neglected with no priority and they do not have any expectation for eradication of NTDs without any information from Japan or other developed countries. As contribution for sustainable education of health and environment for eradication of NTDs with birth control from Japan was remarkable, we better contribute on the same line for eradication of NTDs through education for improvement of health and environment or better quality of life as a sustainable projects combined with bilateral or multilateral governmental economic cooperation or even business. Similar strategies from Europe and USA appear to be much better from the viewpoint of sustainable contribution for the long term.

CONCLUSION

Taeniasis/cysticercosis due to *T. solium* is neglected NTD in Asia or in the world: 1) Eggs of *Taenia* species including two other species are impossible to be differentiated microscopically. 2) The percentage of egg positive cases in any community based survey is far less than any other NTDs such as STHs or FBTs or schistosomiasis. 3) Based on 1) and 2), there is no further studies on T/C. 4) PZQ has widely been recommended for mass treatment of trematodiases and even of cestodiases including taeniases. However, as areas endemic of these NTDs are expected to be veiled T/C endemic areas with no or almost no data, we are afraid of accidental sudden death after PZQ treatment.

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