REVIEW

TAENIASIS AND CYSTICERCOSIS IN ASIA AND THE PACIFIC: PRESENT STATE OF KNOWLEDGE AND PERSPECTIVES

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Abstract. Several topics on taeniasis and cysticercosis in Asia and the Pacific are overviewed. In Asia and the Pacific, three human taeniid species have been recognized: *Taenia solium*, *Taenia saginata* and *Taenia asiatica*. The first topic is on evolution of *T. solium*. Mitochondrial DNA polymorphisms of *T. solium* worldwide are discussed with emphasis of two specific genotypes: American-African and Asian. The second topic is recent major advances in sero- and molecular-diagnosis of *T. solium* cysticercosis in humans, pigs and dogs. The third is the present situation of *T. solium* taeniasis/cysticercosis in Papua (Irian Jaya), Indonesia. The forth is the present situation of *T. solium* cysticercosis and *T. saginata* taeniasis in Bali, Indonesia. The fifth is the present situation of *T. asiatica* taeniasis in Asia and the Pacific and in North Sumatra, Indonesia. The sixth is on the debate of the exact definition of *T. asiatica*. Because *T. asiatica* can not be differentiated from *T. saginata* morphologically, it is time to re-evaluate *T. saginata* in Asia and the Pacific. New and broad-based surveys across this region are necessary from epidemiological and public health perspectives, based on evidence.

INTRODUCTION

Infections in humans with the adult tapeworms of *Taenia* spp (taeniasis) and with the metacestode stages of these parasites (cysticercosis) are recognized in countries in Asia and the Pacific (Cross, 1991; Simanjuntak *et al*, 1997; Singh *et al*, 2002; Wandra *et al*, 2003; Ito *et al*, 2003, 2004a). As their epidemiology in Asia and the Pacific has not been the subject of substantial scientific investigation, our understanding of this disease complex has improved recently following the recognition that a third species (*T. asiatica*) infects humans in Asia and the Pacific. This species is in addition to the well-known pork tapeworm, *T. solium*, and the beef tapeworm, *T. saginata*. It has been recognized in Asia and the Pacific that *T. saginata* infection can be detected in people who ate not only beef but also pork, thus giving us a puzzle of Asian *Taenia* (Inaba, 1924; Yokogawa and Kobayashi, 1928; Park and Chyu, 1963; Kang *et al*, 1965; Huang *et al*, 1966; Kosin *et al*, 1972). The unique life cycle of Asian *Taenia* was first experimentally demonstrated in Taiwan by Fan and his colleagues (Fan *et al*, 1986; Fan, 1988). In contrast to *T. saginata*, pigs act as the intermediate host, where infective metacestodes (MCs) develop in the liver. The MCs in pigs have only rudimentary or vestigial hooks, but adult tapeworms lack rostellar armature (Fan, 1988). It appears to be similar to *T. saginata* in this regard. Also, it has been confirmed that mitochondrial DNA sequencing data of *T. asiatica* is very close to *T. saginata* (Zarlenga *et al*, 1991; Bowles and McManus, 1994; Nakao *et al*, 2002). Based on such molecular information, Fan preferred to keep it as a subspecies of *T. saginata* (Chao *et al*, 1988; Fan *et al*, 1995). Eom and Rim (1993) suggested that this parasite represented an independent species – *T. asiatica* – and provided the first full description with a justification for recognizing and naming the species. From a taxonomic view point, it is not acceptable for us to expect that there are two subspecies of *T. saginata* in Asia and the Pacific. If such subspecies co-exist, it is the same species with some genetic differences and such differences do not function as a barrier for sexual segregation between them. Therefore, it is clear that there are two sister species in Asia: *T. saginata* and *T. asiatica* (Hoberg *et al*, 2001). According to the criteria for the speciation of discrete biological entities, *T. asiatica* is expected to be an independent species (Hoberg *et al*, 2002), but this point is still under debate. Such debate appears to be based not on scientific data but rather on feeling that these two are very close to each other (reviewed by McManus and Bowles, 1994; Ito *et al*, 2003, 2004a). In this brief review, we will discuss several topics based on our own collaborative work in Asia and the Pacific.

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TOPIC 1: TWO GENOTYPES OF *TAENIA SOLIUM* WORLD WIDE

Several groups reported the partial and/or full length of mitochondrial DNA sequences of taeniid species, including *T. solium*, *T. saginata*, *T. asiatica*, *Echinococcus granulosus* and *E. multilocularis* (Bowles and McManus, 1994; Le *et al*, 2000; Okamoto *et al*, 2001; Ito *et al*, 2002a; Nakao *et al*, 2002). With *T. solium*, it has become clear that specimens of *T. solium* worldwide can be differentiated into two genotypes: American-African and Asian (Okamoto *et al*, 2001; Ito *et al*, 2002a; Nakao *et al*, 2002). According to Hoberg and colleagues (2001), *T. solium* emerged in Africa several million years ago as human parasite (*Homo erectus* or early *Homo sapiens*) and the life cycle was completed by cannibalism and moved to Eurasia. Nakao and colleagues (2002) found that (1) *T. solium*, distributed worldwide nowadays, are divided into American/African and Asian genotypes and speculated that (2) the original genotype of American/African is a European genotype, and that (3) European and Asian genotypes of *T. solium* were expected to have emerged approximately one million years ago. *T. solium* helminthes distributed in Africa and Latin America are suspected to have been introduced from Portugal and Spain 500 years ago (Ito *et al*, 2002a; Nakao *et al*, 2002).

Where can we get the European genotype of *T. solium*? It is almost impossible to obtain *T. solium* of European origin and even if we can obtain specimens from taeniasis or cysticercosis in Europe, it does not indicate that such specimens are of European origin. When we visited European institutions several times, almost all specimens of *T. solium* kept for demonstration with data were expelled from Asian people. However, in some areas in Central Asia and Mongolia and Russia, *T. solium* cysticercosis is still not so rare. Examining mitochondrial DNA of *T. solium* from these areas might be highly interesting and informative.

TOPIC 2: MAJOR ADVANCES IN SERO- AND MOLECULAR DIAGNOSES OF CYSTICERCOSIS OF *TAENIA SOLIUM* IN HUMANS, PIGS AND DOGS

2-A. Human cysticercosis of *T. solium*

There are two strategies for detection of patients infected with *T. solium* MCs: detection of specific antibodies or circulating antigens (Ito, 2002; Ito *et al*, 2002b, 2004a; Ito and Craig, 2003; Dorny *et al*, 2003). Although both strategies may be expected to be complementary, we focused on the recent advances in detection of antibodies. Pioneer work showing species-specific bands by immunoblots was achieved by Gottstein *et al* (1986) and Parkhouse and Harrison (1987). Based on such work, Tsang and colleagues (1989) showed better resolution for preparation of specific antigens suitable for serodiagnosis. There are basically three methods for purification of specific glycoproteins (GPs) of MCs of *T. solium*: immunochromatography using monoclonal antibody (Kim *et al*, 1986), affinity chromatography using lentil lectins (Tsang *et al*, 1989) and iso-electric focusing (Ito *et al*, 1998). The gold standard for detection of cysticercosis in humans over the past decade was immunoblot (IB) using purified GPs. However, ELISA with very similar sensitivity and specificity as IB is now available and applicable not only for humans but also for pigs and dogs (Ito *et al*, 1998, 1999, 2004a; Subahar *et al*, 2001; Sato *et al*, 2002; Ikejima *et al*, 2004). Alternative approaches for improvement of serology is challenged by production of recombinant antigens (Chung *et al*, 1999; Green *et al*, 2000; Sako *et al*, 2000) and synthetic peptides (Chung *et al*, 2002; Ito *et al*, 2002a; Ito *et al*, 2002a; Hancock *et al*, 2002). Thus far, sensitivity of recombinant antigens or synthetic peptides appears to be not as high as native antigens (Chung *et al*, 2002; Hancock *et al*, 2003; Sako unpublished). Several groups have succeeded in preparation of highly specific and sensitive diagnostic antigens, even though they do not always provide such good antigens for other research groups.

2-B. Swine and canine cysticercosis of *T. solium*

There are several reports on detection of specific antibodies in pigs infected with MCs of *T. solium* (Ito *et al*, 1999; Subahar *et al*, 2001; Sato *et al*, 2002). Detection of pigs experimentally infected with various numbers of viable eggs has also been reported (Sato *et al*, 2002). Due to our own experience, the GPs purified by immunoaffinity chromatography (Kim *et al*, 1986), by lentil lection chromatography (Tsang *et al*, 1989) and by iso-electric focusing (Ito *et al*, 1998) were all highly reliable for detection of active cysticercosis cases in humans, pigs and dogs (Subahar *et al*, 2001; Ito *et al*, 2002b; Sato *et al*, 2002). It has been known that dogs may be infected with MCs of *T. solium*. Application of ELISA and IB for detection of dogs infected with MCs of *T. solium* was carried out in Irian Jaya. Approximately 10% of local dogs sampled at random were found to be sero-positive. Based on the serological data, several dogs were killed and all sero-positive dogs examined were confirmed to have harbored MCs of *T. solium* (Fig 1) (Ito *et al*, 2002c).

Fig 1- A local dog full of cysticerci of *T. solium* which was suspected to be infected with cysticerci of *T. solium* by both ELISA and IB using both native and recombinant antigens with molecular confirmation (Ito *et al*, 2002).

2-C. Molecular tools for identification of human taeniid specimens

Based on the sequence of mitochondrial DNA of taeniid species (Zarlenga *et al*, 1991; Bowles and McManus, 1994; Nakao *et al*, 2000, 2002, 2003; Okamoto *et al*, 2001; Le *et al*, 2000, 2002), several new simpler tools for molecular identification of human taeniid specimens have been developed (Yamasaki *et al*, 2002, 2004a, b; reviewed by Ito, 2002; Ito and Craig, 2003). Such DNA identification is highly useful with combination of copro-antigen tests for taeniasis of *T. solium* (Allan *et al*, 1990) as well as *T. saginata* (Deplazes *et al*, 1991).

TOPIC 3: *TAENIA SOLIUM* TAENIASIS/ CYSTICERCOSIS IN IRIAN JAYA, INDONESIA AND IN PAPUA NEW GUINEA (PNG)

Cysticercosis of *T. solium* has historically been recognized in Bali, Indonesia (Simanjuntak *et al*, 1997; Sutisna *et al*, 1999; Margono *et al*, 2003, 2004). However, the most serious focus of cysticercosis of *T. solium* in Indonesia is in Papua (Irian Jaya), Indonesia. After the first report of *T. solium* cysticercosis from Papua by Tumada and Margono (1973), there are several original reports showing the seriousness of this disease in Papua (reviewed by Simanjuntak *et al*, 1997; Ito *et al*, 2003, 2004a,b). Indonesian groups did excellent and hard field surveys from 1991 to 1995. Analysis of antibodies specific to cysticercosis and molecular identification of resected cysts from local people were carried out in collaboration with the Asahikawa group (Wandra *et al*, 2000). Further studies have been conducted since 1997 as Indonesia-Japan collaboration projects in Papua, Sumatra and Bali (Wandra *et al*, 2003; Ito *et al*, 2004a,b). Approximately 70% and 83% (respectively) of local residents who had (1) a history of epilepsy and (2) a history of epilepsy plus subcutaneous nodules were serologically confirmed to have been exposed to *T. solium* in Assologaima, Jayawijaya, Papua. Subcutaneous nodules from antibody-positive people were confirmed to be MCs of *T. solium* (Asian genotype) (Ito *et al*, 2004a).

Because approximately 3% of local residents in Dome Village, Papua New Guinea were serologically confirmed to have been exposed with *T. solium* (Wandra *et al*, 2003; Ito *et al*, 2004b, in press), it was crucial to detect pigs infected with *T. solium* in PNG (Fritzsche *et al*, 1990; McManus, 1995; Flew, 1998). As far as we know, there is no pig infected with *T. solium* (Puana I and Owen IL, personal communication). It is pointed out that cysticercosis of *T. solium* should be investigated carefully in PNG, East Timor and several other islands, including West Timor in Indonesia, where the majority of people are Christians who eat pork (Suroso, 2000; Wandra *et al*, 2003; Ito *et al*, 2004a). In East Timor, one taeniasis case of *T. solium* has been confirmed (personal communication from D Reeve, JCU in Australia). If it is sound, there is no doubt that cysticercosis cases will be confirmed from humans and animals, including pigs and dogs.

TOPIC 4: *TAENIA SOLIUM* CYSTICERCOSIS AND *TAENIA SAGINATA* TAENIASIS IN BALI, INDONESIA

A favorite dish of the Balinese is "Lawar" (minced uncooked pork with blood). As Balinese have well-organized community "Banjar," during which they share meals, including such uncooked pork, if the meal is contaminated with pathogens, it easily becomes a public health issue. This scenario is true for *T. solium* cysticercosis in Bali. However, nowadays, it is very rare to detect cysticercosis in humans and pigs in Bali. The most important factor for the success in eradication of *T. solium* cysticercosis is based on educating the public to keep pigs indoors and cut off their free access to human feces. There is no pig that is not kept indoors in Bali (Sutisna *et al*, 1999; Wandra *et al*, 2003, Ito *et al*, 2004a,b). In contrast, taeniasis of *T. saginata* is rather common (Sutisna *et al*, 1999). In several districts, infection rates of *T. saginata* in humans are as high as 27%. When we did field surveys in 2002

and 2004 in Bali, we found approximately 25.6% (32/125 in 2002) and 27.5% (14/51 in 2004) of villagers were infected with *T. saginata* (Wandra *et al*, in preparation). It was interesting and important that all 32 persons who were treated with praziquantel in 2002 had no more tapeworms when they were re-checked in 2004. All had stopped eating uncooked beef after they recognized that they harbored big tapeworms in their intestine. All taeniid specimens that we could analyze were *T. saginata* exclusively. Thus, we could detect no *T. asiatica* or *T. solium* at all in Bali during our 2002 and 2004 surveillance. This may be explained because both species require pigs as the intermediate host. Because Bali is one of the most world famous resort areas, it is an important issue to control taeniasis in the local people in order to prevent infection of travelers.

TOPIC 5: *TAENIA ASIATICA* IN ASIA AND THE PACIFIC

5-a. Where is *T. asiatica* distributed in Asia and the Pacific?

As far as we know, *T. asiatica* has been found from Taiwan (Fan, 1988), mainland China (Eom *et al*, 2002; Yamasaki *et al*, 2004a), Korea (Eom and Rim, 1993), Indonesia (Kosin *et al*, 1972), Philippines (Fan *et al*, 1992; Bowles and McManus, 1994; Leon *et al*, in preparation), Malaysia (Bowles and McManus, 1994), Thailand (Fan *et al*, 1990), and Vietnam (Willingham *et al*, 2003; reviewed by Ito *et al*, 2003, 2004a).

5-b. *T. asiatica* in North Sumatra, Indonesia

Kosin *et al* (1972) reported Asian Taenia from Samosir Island in Lake Toba, north Sumatra. In this area, minced uncooked pork with viscera called "Sang-Sang" is popular. As far as we know, *T. asiatica* is exclusive to Samosir Island. However, there is no formal information of epilepsy there. Thus, we are hesitant to check if *T. solium* is distributed there or not (Depary and Kosman, 1991). Ten years ago, it was very easy to detect taeniasis cases of *T. asiatica* there (Depary's personal communication). But when we did a field survey in 2002, we could find only two patients with taeniasis. One reason for the drop in numbers of taeniasis in Samosir Island may be ascribed to cooking pork (Wandra *et al*, unpublished). These recent data strongly suggest that there are two strategies for the cut-off of the life cycle of *T. solium* or *T. asiatica* through sustainable public health education. One is to keep pigs separate from human feces by keeping pigs indoors, and the other is to cook pork and viscera well (Schantz *et al*, 1993). Are these public health strategies applicable or feasible in Papua for control of cysticercosis? We do not believe that such strategies are feasible in Papua at this stage. It takes several decades for sustainable public health education. Anyway, we should start some action to challenge this public health issue with funding from WHO, FAO or others. Simultaneously, more detailed surveillance is essential to know about the present situation in areas where historical outbreaks were reported in the early 1970's in Papua (Simanjuntak *et al*, 1997; Wandra *et al*, 2003).

TOPIC 6: WHAT IS *TAENIA ASIATICA*?

This is still under debate as to whether it is a real independent species or subspecies of *T. saginata* (Ito *et al*, 2003a, 2004a). Based on the criterion for taxa, it is highly suggestive to be an independent species (Eom *et al*, 1993, 2002; Hoberg *et al*, 2000, 2002; Ito *et al*, 2003a, 2004a). It is fruitless to debate without any additional data. Some researchers expect that it is a subspecies of *T. saginata* (McManus and Bowles, 1994; Ito and Craig, 2003). Basically, we also have such a feeling. However, we have to show some additional evidence of hybrids of the two in order to refute it. Human taeniid species are based on our consumption of beef and pork. However, such eating customs may highly be restricted by culture, especially through religions. Such contaminated beef and pork with viscera are only available in remote areas in developing countries. Thus, it is very unlikely for us to expect persons are harboring both (*T. saginata* and *T. asiatica*) in their intestines. If we have the unexpected luck to detect hybrids of these from remote areas, we can stress that they are subspecies. However, such a finding seems unlikely. What is an alternative way for acquiring additional data for the debate? It would only be through experimental double infection in volunteers. As MCs of any human taeniid species can easily develop in immunodeficient mice (Ito and Ito, 1998; Ito *et al*, 2001, 2004a), we can use viable eggs to cultivate MCs in such mice. When MCs of both are available, volunteers would have to ingest a single MC from each species. When proglottids emerge from the volunteer's anus, eggs would have to be prepared and used for production of the second generation of MCs. Therafter, we would have to check microsatellite DNA for identification of hybrids, since Nakao *et al* (2003) revealed that cestodes can exhibit selfing and out-crossing using microsatellite DNA markers in *Echinococcus multilocularis*. Who can do such long-span work for the debate of this issue? Thus, this debate will remain an unresolved problem without further scientific contribution (Ito *et al*, 2004a).

CONCLUSION

In Asia, we have *Taenia solium*, *Taenia saginata* and *Taenia asiatica*. It is still under debate if *Taenia asiatica* is an independent valid species or subspecies. Because selfing and out-crossing may occur in cestode infections (Nakao *et al*, 2003), it may only be possible to reach a conclusion after experimental infection in volunteers with single cysts (cultivated in immunodeficient mice) of *T. saginata* and *T. asiatica*. Microsatellite DNA markers useful for differentiation of these two species or subspecies are crucial.

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