ECHINOCOCCOSIS AND CYSTICERCOSIS IN ASIA: EVALUATION OF THE MODERN TECHNOLOGY FOR EPIDEMIOLOGICAL STUDY

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Abstract. The recent emergence of zoonotic parasitic diseases of public health importance represents a growing global concern. Among zoonotic helminthic diseases, both echinococcosis and cysticercosis are the most serious diseases threatening human life. Neurocysticercosis (NCC) caused by ingestion of eggs of the pork tapeworm, *Taenia solium*, is spreading worldwide and not rare even in Muslim or Jewish communities. Alveolar echinococcosis (AE) caused by the proliferation of metacestodes of the fox tapeworm, *Echinococcus multilocularis*, is the most potentially lethal parasitic infection of the non-tropical northern hemisphere, whereas cystic echinococcosis (CE) caused by the proliferation of metacestodes of the dog tapeworm, *E. granulosus*, has rather a cosmopolitan distribution. As the life cycles of *T. solium, E. multilocularis* and *E. granulosus* are completed through predator-prey interactions, including humans, it is crucial to interrupt the cycle for control of these zoonotic cestodiases. Both NCC and CE are expected to be eradicable, since the principal life cycles of *T. solium* and *E. granulosus* are maintained between humans and pigs and between dogs and herbivorous domestic animals, respectively. In contrast, AE is perhaps not eradicable, since the life cycle of *E. multilocularis* is maintained between wild foxes and rodents. Modern technologies, including imaging, immunology and molecular biology, have been applied for epidemiological surveys. In the present review, we introduce such technologies applied in Japan, China and Indonesia, and point out the problems that need to be solved for control of these three zoonotic cestodiases.

INTRODUCTION

Although we employ serological tests for cestode zoonoses, including neurocysticercosis (NCC) caused by the pork tapeworm, *Taenia solium,* alveolar echinococcosis (AE) caused by the fox tapeworm, *Echinococcus multilocularis*, and cystic echinococcosis (CE) caused by the dog tapeworm, *Echinococcus granulosus*, during the previous JITMM and/or Food-borne Parasitic Zoonoses meetings (Ito, 1997; Ito *et al*, 2000, 2001a,b, 2002a) and some other meetings (Ito *et al*, 2002b,c), we have reported much improved such technologies for the serodiagnosis, immunodiagnosis and molecular diagnosis of these cestode zoonoses. There are several excellent up-to-date reviews on the advances in technology for these cestode zoonoses (Eckert *et al*, 2000; Siles-Lukas and Gottstein, 2001; Ito, 2002; Ito and Craig, 2003). In the present review, we introduce: 1) the pathology of these three cestode zoonoses; 2) recent advances in serodiagnosis, immunodiagnosis and molecular diagnosis, and 3) applications for epidemiological surveys for these cestode zoonoses based mainly on our own work at Asahikawa Medical College (AMC).

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PATHOLOGY OF NCC, AE AND CE

Pathological characteristics

NCC is mainly a neurological disease and differs critically from echinococcosis, either AE or CE, which are hepatic diseases. However, neuro-echinococcosis may be not so rare in some highly endemic AE areas, such as in China. Major symptoms of NCC are seizures, focal neurological deficits, symptoms of increased intracranial pressure, and dementia. In the computed tomography (CT) and magnetic resonance imaging (MRI) scan, the nodule in the brain appears to be a round cyst with contents near water density and a hyperdense scolex. However, only approximately 10% of NCC may show such typical imaging data (Del Brutto *et al*, 1998). In Papua in Indonesia, the majority of NCC patients have subcutaneous nodules of cysticerci (subcutaneous cysticercosis, SCC) of *T. solium* simultaneously. It is expected that SCC-suspected patients are asymptomatic for NCC (Wandra *et al*, 2003). In contrast, both AE and CE are hepatic diseases. AE appears to be like hepatic cancer. In the

CT scan, and ultrasonography (US) hepatic AE lesions are characterized by heterogenous hypodense masses, often associated with necrotic cavities. In contrast, a CE lesion usually presents as a single cyst, which is round or spherical, with contents near water density. If the cyst has daughter cysts inside, the US and CT reveal honeycomb-, rosette- or water lily-like structures (Xu and Ito, 1995; Ito *et al*, 1998; Pawlowski *et al*, 2001).

Although CT and MRI scans and US are highly informative of suspected NCC, CE and AE, it is difficult to diagnose non-typical cases correctly. Therefore, a combination with some other strategy is crucial. The most important and reliable non-invasive technology is serodiagnosis. The specificity and sensitivity of serology for these cestode zoonoses has been improved greatly in the past decade and almost 100% specific serodiagnosis for these three cestode zoonoses is available (Ito *et al*, 2001b; Ito and Craig, 2003). Due to the high cost of imaging analysis, serodiagnosis is the first choice for these diseases followed by CT or MRI scanning to confirm the active lesions, if necessary.

TREATMENT

NCC

Although praziquantel or albendazole has been recommended for the chemotherapy of NCC, there is debate about its necessity. Most symptoms come from the initiation of destruction or killing of the parasite after the host defense mechanisms become stronger than the parasite defense mechanisms. Therefore, the onset of symptoms is considered to be the signal for imminent parasite death. Similarly, there is debate concerning the chemotherapy of taeniasis patients harboring adults *T. solium*. The most recent recommendation is the use of praziquantel at lower doses (5 or 10 mg/kg single) (Sarti *et al*, 2000; Ito *et al*, 2003b).

AE

Radical surgery of hepatic lesions is only recommended to date. Therefore, early detection (early diagnosis) of hepatic AE is crucial. In Japan, complicated AE cases with lesions in the liver, lung and bone are not rare. In such complicated cases, if radical surgery is applicable for an active lesion, it is done with continuous albendazole treatment.

CE

PAIR (puncture, aspiration, injection and re-aspiration) is recommended for CE cases with no fistula with bile duct by WHO-IWGE (informal working group on echinococcosis). CE lesions(s) in younger patients are more susceptible to chemotherapy with benzimidazoles, including albendazole, although the rate of relapse after chemotherapy is not so low (Pawlowski *et al*, 2001; WHO-IWGE, 2001).

EPIDEMIOLOGY

There is no real evidence-based epidemiology without a reliable strategy or technology. If the techniques are not very reliable, the outcome is overestimation, confusion, anxiety and expense in persons whose specimens give false positive results (Ito *et al*, 2003a).

NCC in Asia

So far, the worst areas for NCC in Asia have been identified as Papua in Indonesia (Margono *et al*, 2001; Singh *et al*, 2000). NCC became endemic in Papua after 1969, when it was governed by Indonesia. The endemic areas have spread from central Paniai District to east Jayawijaya District and to west Manokwari (Wandra *et al*, 2000). Recent surveys in Jayawijaya by Prof Margono (University of Indonesia) and Dr Suroso, (Department of Communicable Disease Control and Environmental Health, Ministry of Health, Jakarta with collaboration of AMC), have confirmed that approximately 46% of local people from Jayawijaya are suffering from NCC (Margono *et al*, 2001). Most of them also have subcutaneous nodules and these nodules are due to *T. solium* cysticerci. Therefore, it is expected that such subcutaneous cysticercosis patients are asymptomatic of NCC (Wandra *et al*, 2000, 2003; Subahar *et al*, 2001; Margono *et al*, 2003). Not only pigs, but also local dogs are infected with cysticerci and easily confirmed by serology (Subahar *et al*, 2001; Ito *et al*, 2002d).

What is likely to happen in Papua New Guinea (PNG)? Approximately 3% of local residents and Papuan refugees along the border (Alice River Villages) have been serologically confirmed to have asymptomatic cysticercosis (Ito *et al*, unpublished).

Based on the high populations, NCC is much more serious in both China and India. In China, special hospitals for cysticercosis are not rare. In India, solitary cysticercosis is more common, although the majority of people are vegetarians (Singh *et al*, 2002). Serology established at AMC is applied for the evaluation of NCC serodiagnosis, especially solitary NCC cases.

Echinococcosis in Asia

The seriousness of AE has become evident in Japan and China. In China, both AE and CE are highly

endemic in some remote areas and an international project on the ecology and epidemiology of echinococcosis is underway (October 2000-September 2004) sponsored by the US-NIH (principal investigator: Craig PS). A national surveillance project on these diseases nation-wide is also ongoing. There are many AE and CE, and double-infected AE/CE, cases in Tibetan people living in Sichuan, Qinghai, where the dog is the most important risk factor for transmission of AE to humans (Craig *et al*, 2000). For such epidemiological surveillance, both US and serology (ELISA using cyst fluid of *Echinococcus granulosus* EgCF-ELISA, and Em18-ELISA) have been used (Ito *et al*, 2002c).

In Japan, a two-step system for the detection of AE patients has been established by the local government in Hokkaido. The first step is serology by ELISA using crude antigens of *E. multilocularis* for primary screening, and the second is serological confirmation of AE by immunoblot using crude antigens. However, when we at AMC were asked to check such AE patients suspected through the two steps, we found approximately 20% of them were not AE cases using Em18 serology (Ito *et al*, 2003a). At the beginning of November 2002, there was an international conference on "The Emerging Infectious Diseases in The Pacific Rim" held in Shanghai, China. One speaker from Japan summarized the present AE epidemic situation in Japan, and stressed that the ongoing system to detect human AE cases is not functional and unreliable due to the lack of scientifically sound, reliable data on the epidemics in Hokkaido or elsewhere in Japan. This is why it is necessary to introduce more reliable techniques for the identification of AE patients and analyze the pathologic dynamics.

In the USA, there were only two human AE cases, reported over 30 years ago. There has been no human AE case from the USA or Canada, except for Alaska, for the past three decades, although 60-90% of wild animals, such as foxes and coyotes are infected with this parasite (Storandt *et al*, 2002). In Hokkaido approximately 40-60% of foxes are infected. There are two speculations for the future AE situation in Japan. One is that there should be more AE cases due to the high contamination of the environment by the fox. The other is that AE is an accidental infection under poor hygiene conditions, and the number of AE cases does not increase, although there may be some accidental new cases. No one knows the real situation, even in Europe, where more research using techniques with higher reliability than in Japan has been carried out over a much longer term.

CE is spreading worldwide. As the life cycle is maintained between dogs and sheep or other cattle, if the life cycle becomes established in countries where there is no indigenous case, it becomes a public health problem. In Asia, CE is the most serious in China (Craig *et al*, 1991; 1992; 2000; 2002; Wen *et al*, 2002; Ito *et al*, 2003b), India and Nepal (Eckert *et al*, 2001). However, it is expected that sporadic CE cases may occur in any country including Bangladesh, Indonesia or the Philippines, where the lifecycle may be introduced or established, at least temporarily. More common sporadic CE cases in countries where CE is non-indigenous are imported, such as in Korea, from endemic countries such as the Middle East after the Gulf War. During the last five years, there have been at least 5 imported CE cases in Japan, one from Jordan, one from Nepal, one from Argentina (Japanese man born there and lived until age 5 years) and two from China.

Conclusion

In order to obtain highly reliable data for infected persons and infected animals for the control of these cestode zoonoses, the establishment of highly reliable strategies and technologies is crucial. If we apply only moderately reliable strategies including immunological tests using crude antigens or antigens with only moderate specificity, the outcome will be overestimation, confusion, anxiety and expense in persons whose specimens give false positive results. Such unreliable data, not based on sound evidence, is often used for propaganda, to agitate the fearful mess, not only in Europe, but also in Asia, including Japan and elsewhere. We must improve the technology and the science, and show high standard evidence as far as possible, and confirm it through evidence-based medical science.

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