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Outbreak Investigation Express

A Norovirus Outbreak in a Primary School, Hwalien County, 2010

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Abstract

In the morning on November 25th, 2010, the school nurse of School A reported 13 students were on sick leave. She noticed that most students including teachers in the class had vomiting and diarrhea. Thus, the local Bureau of Health, the Sixth Branch of Taiwan Centers for Disease Control (TCDC) and Eastern Regional Office of Taiwan Food and Drug Administration (TFDA) initiated epidemiologic investigation and identified six schools and institutes were involved in this outbreak. Strict measures including increase social distance, high frequency hand washing and environmental disinfection were implemented and the outbreak was blockaded at the second wave in all but the School A. Among the 62 human and 3 food specimens collected during the surveillance period, 10 stool specimens were tested positive for norovirus. According to the symptoms, the incubation period and test result of case-patients, this outbreak was regarded as a norovirus infection. Initially, this outbreak

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INSIDE

occurred in the primary school A with a common source and then subsequently transmitted into epidemiologically linked schools and institutes and led to small scale clustering. In addition to contact a patient and handling vomitus, our research indicated that the spatial distance to a case-patient with vomiting was positively correlated to the date of onset, it implied that invisible droplets might mediate contact infection, and reemphasized the importance of hand washing and high frequency environmental disinfection.

Key words: norovirus, clustering, outbreak

Original Article

Epidemics of Toxoplasmosis in Taiwan

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Abstract

Toxoplasmosis has become one of the 4th category of National Notifiable Communicable Diseases in Taiwan since 2007. Among the 143 patients reported during 2008-2010, 68 cases were serologically positive for toxoplasma infection and 15 of them were primary infections. One patient with congenital infection was identified, vertical transmission from mother who might have ingested contaminated raw pork to the fetus was suspected. Toxoplasmosis is a zoonotic disease caused by the protozoan *Toxoplasma gondii*. The clinical presentation is more severe among immunocompromised patients and those with congenital infection; the subsequent medical and associated expenditure is enormous. Therefore, education targeting not only childbearing-aged women, but also general population should be reinforced. Physicians should be more alert and notification of suspected cases should be encouraged. This article addressed the current epidemics of toxoplasmosis in Taiwan, and also discussed the surveillance system in European countries. The later can be references for establishing our own surveillance system and control measures.

Keywords: Toxoplasmosis, zoonosis

Introduction

Toxoplasma gondii is a ubiquitous intracellular parasite, belonging to the subphylum Apicomplexa, and is capable to infect most warm-blooded animals [1]. The primary host is the felid family (cats), and other warm-blooded animals, including humans, are infected by ingestion of food and water contaminated by sporulated oocyst in cat feces, or by ingestion of tissue cyst in raw contaminated meat [1].

Toxoplasma gondii has three different stages. Oocyst only exists in felid family (cat) and belongs to sexual cycle. Tachyzoite (a rapidly dividing form) is more common among patients with acute infection while bradyzoite (the slow growing form) can survive for a long time in tissue cysts after the emergence of host immunity [2].

The asexual cycle occurs in warm-blooded mammals, but the sexual cycle only occurs in epithelial cells of small bowel of the felid family. Macrogametocyte and microgametocyte fuses to form oocyst, which is shed with feces. It takes 24 to 48 hours for oocyst to sporulate and become infectious. Warm-blooded animals ingest the sporulated oocysts, which then enter the nearby lymphatic tissues and become tachyzoites and form tissue cysts in brain, retina, striated muscles, and hepatocytes. The tissue cysts contain hundreds of bradyzoites, resulting in latent infection. Once the host immunity decreases, the cysts will rupture and bradyzoites will be released and will cause relapse of infection [2].

Clinical presentation and epidemiology

Severe diseases caused by *Toxoplasma gondii* are not common, except in those with congenital toxoplasmosis or in those with compromised immunity. All organ systems could be involved, especially central nerve system, eyes, lymph nodes, heart, lungs, liver and muscles. People can acquire infection by ingestion of raw or undercooked meat, including beef, and pork, by food or water contaminated by *Toxoplasma gondii* oocysts in the feces, by vertical transmission through placenta, by blood transfusion, or by organ transplantation [2]. For patients with normal immunity, the infection is often asymptomatic though few people could have lymphadenopathy, retinochoroiditis in acute stage. The earlier the infection during pregnancy, the greater the influence is on fetus. Spontaneous abortion or stillbirth may occur. If pregnant women acquire infection during the first trimester, 80% of the newborns will have congenital toxoplasmosis, presenting with generalized lymphadenopathy, hydrocephalus, microcephaly, neurologic disorders, and retinochoroiditis that may result in blindness. Twenty percent of those with congenital toxoplasmosis can be asymptomatic at first; decreased visual acuity, disability in learning, and metal retardation may gradually develop in months [2]. For patients with compromised immunity, neurologic disorders such as encephalitis are most common [3].

Allogeneic organ transplantation may result in toxoplasmosis in recipient, though the mechanisms are different in solid-organ transplantation (SOT) and in hematopoietic stem cell transplantation (HSCT). In SOT, recipients acquire infection from donors who have been infected, especially when the organ is the one that *Toxoplasma gondii* is prone to reside, such as heart or lung. In HSCT, most recipients get toxoplasmosis by re-activation of latent infection. If the donor does not have acute infection and parasitemia, the risk of getting infection from a donor's hematopoietic stem cell is low. In addition, use of immune-suppressants is more aggressive in HSCT than in SOT, so the risk of disease reactivation is higher [4].

The prevalence and risk factors of getting infection are different geographically. The seropositive rate is about 22.5% in the United States [5], 30 to 80% in European countries [6], 75% in France [7], 59% in Brazil [7], 35% in Mexico [7], 58% in Indonesia [8], and 2.3 to 21.9% in Thailand [9-10]. In a case-control study conducted in European countries (including Belgium,

Denmark, Italy, Norway, Switzerland, and England), ingestion of raw or undercooked meat is the most important risk factor, and the type of meat at risk is different because of cultural differences in different countries [11]. In Central and South America, people eat cooked food, so the risk factor of infection is not the same as in Europe. In Mexico and Brazil, because there are many street cats that are often fed with raw meat and raw visceral organs, and because the weather there is suitable for oocysts to survive, contact with cat feces is the major transmission route [12]. In the United States, the more the cats get infection, the higher the human infection risk is. Contact with contaminated soil may be the common route [13].

Diagnostic methods

The anti-toxoplasma-specific IgM can be identified 1 to 2 weeks after infection, followed by the appearance of IgA and IgE [14]. The peak of the aforementioned antibodies usually occurs within 2 months. Although IgM can sometimes be found for years, the others usually disappear gradually [15]. IgG can be detected after IgM, its titer peaks within 4 months and declines to a steady level in 12 to 24 months [15].

Because the clinical presentations of toxoplasmosis are various and non-specific, and because healthy person can be asymptomatic or only has minor illness after infection, diagnosis cannot be made only based on symptoms. The key point of laboratory diagnosis is to differentiate if a suspected patient has recent infection. Serologic study is reliable and polymerase chain reaction (PCR) can also be helpful. Generally speaking, anti-toxoplasma-specific IgG, IgM, and IgG affinity tests should be performed. If IgG and IgM are both positive and the affinity of IgG is high, recent infection within 3 o 4 months can be ruled out [16]. In neonates, not only IgG, IgM, and IgA should be tested, PCR of umbilical blood or amniotic fluid should be performed, too. Because maternal IgG pass through placenta, detection of IgM and IgA is more reliable [17]. Differentiation between maternal IgG from neonatal IgG can be made by Western blot method [16]. In immune compromised hosts, tissue samples from infection focus or cerebrospinal fluid should be taken and tested using PCR to detect pathogen-specific genes; patients' clinical presentations and images of brain computer tomography should be compatible [18].

Serologic studies can be performed by Sabin-Feldman dye test [19], latex agglutination test [20], indirect fluorescent antibody test [21], and enzyme-linked immunoassay (EIA) [22]. PCR can be performed by amplification of the B1 gene and the 529 bp repeated element (RE) of *Toxoplasma gondii* [23]. In *Toxoplasma gondii*, there were 35 copies of B1 gene [23] and 200 to 300 copies of the RE [24]. Sensitivity can be improved by using nested PCR or real-time PCR.

Epidemiology in Taiwan

Few studies have addressed the incidence and prevalence of toxoplasmosis in Taiwan. In one study conducted by National Taiwan University Hospital in 2006 and 2008, the prevalence among HIV patients was 10.2% and the incidence of Toxoplasma

encephalitis was 0.59 per 100 persons per year [25]. In 1985, Yu *et al.* found that the prevalence of toxoplasma infection in northern and central Taiwan tested by EIA in pregnant women and neonates from 4 hospitals were 10.2% and 11.6% respectively [26]. In 2006, Hu *et al.* also used EIA to detect the seropositive rates in neonates and their mothers in 2 hospitals and 2 obstetrics clinics in northern Taiwan. The seropositive rates among mothers and their children were 9.1% and 9.3%, respectively. Maternal nationality of Mainland China and occupation related to agriculture were identified as major risk factors. Mothers who raised cats had higher IgG titer, but the difference was not statistically significant [27].

In 2001, Fan *et al.* reported the seropositive rates in residents of outlying islands. In Kinmen and Penghu, the prevalence rates were 28.2% and 2.71%, respectively [28]. In 1998, Fan *et al.* found that the seropositive rate in aboriginal people in Nan'ao was 21.8% [29]. Except the aforementioned studies on some specific ethnic groups, investigations targeting general population are few. To make effective control measure, a comprehensive study is necessary.

Toxoplasmosis has been classified as one of the 4th category of National Notifiable Disease since October 2007. A total number of 143 patients have been reported as suspected cases; 68 were seropositive and 15 of them had primary infection. Their age ranged between 0 and 78 with a mean of 38.7 years. As for age distribution, 4 (5.9%) were between 0-15, 17 (25%) were between 16-30, 25 (36.8%) were between 31-45, 14 (20.6%) were between 46-60, and 8 (11.7%) were older than 60 years old. Middle-aged patients were more common. Thirty-seven (54.4%) of the 68 cases were female. Considering the geographic distribution, 38 (55.9%) were found in northern Taiwan, 12 (17.6%) were found in central Taiwan, 17 (25%) were found in southern Taiwan, and 1 (1.5%) was found in eastern Taiwan. Only one patient was from mountain indigenous township. Common clinical presentations at the time of notification of the 68 seropositive cases were lymphadenopathy (20.6%), fever (11.8%), visual problems including retinochoroiditis (10.3%), consciousness disturbance or focal neurologic deficit (7.4%), and other symptoms (29.4%). Twenty patients (29.4%) had animal contact history.

In 2000, one congenital toxoplasmosis was found. The neonate's gestational age of was 37 weeks and brain was found to have calcification and cavitation on brain MRI and ultrasonography. At gestational age 24 weeks, the mother had eaten raw marinated pork. Maternal infection with vertical transmission was highly suspected.

Surveillance and screening

Surveillance systems for toxoplasmosis have been established in European countries between 1960 and 1970 (Table 1). Denmark, France, Germany, and Italy only target congenital toxoplasmosis, while most other countries, such as England and Poland, not only monitor all forms of infection by national surveillance program, but also implement control measures. Italy has toxoplasmosis cases reported sporadically by local social workers and pediatricians but without formal national control programs [30].

Screening policy is also different from country to country because of the difference in incidence. Some included the screening for toxoplasmosis as part of the routine pre-natal examination, such as Austria and France [31]. Pregnant women need to be tested every three months in Austria and every month in France (Table 2). Treatment is initiated once primary infection is identified to decrease the risk of vertical transmission [31]. Neonatal screening is done in Denmark and some States in the America, an 80% of infected neonates could be detected [32-33]. However, because solid evidence supporting the notion that treatment of infected women can reduce vertical transmission or lessen the neonatal symptoms is little, and because the results of observational studies were inconsistent, some countries do not apply routine screening so far [31].

Table 1 Surveillance systems of European countries

Country	Initiation	Target diseases	Target populations	Source of notification	Department in charge
Demark	1999	Congenital Toxoplasmosis (National)	Neonates and women who just give birth	National Serology Center	Department of Health
Germany	2001	Congenital Toxoplasmosis (National)	Neonates, infants, and pregnant women	Reference laboratories	Robert Koch Institute
Italy	1997	Toxoplasmosis during pregnancy, congenital Toxoplasmosis, infected young children with complications (Campania alone)	Fetus, neonates, and infants	Pediatricians, social workers	Department of Health
Poland	1966	Toxoplasmosis	All population	Hospitals and clinics	Department of Health
England	1975	Toxoplasmosis	All population	Reference laboratories	Department of Health
France	2000	Congenital Toxoplasmosis (National)	Fetus, neonates, and infants	Reference laboratories	Department of Health

Source of information: The EUROTOXO Group

Table 2 Screening policies in European countries

Country	Seropositive rate among pregnant women	Screen policy	Timing	Coverage
Denmark	27%	Neonatal screening	At birth	—
Germany	38-73%	None	—	—
Italy	37-41%	Pre-natal screening	Monthly	100%
England	8-19%	None	—	—
France	54-70%	Pre-natal screening	Monthly	100%
Austria	43-50%	Pre-natal screening	Every 3 months	100%
Netherlands	—	None	—	—

"—"：lack of reference Source of information：The EUROTOXO Group

The seropositive rate among pregnant women was about 10% in Taiwan [26,27], but the incidence of toxoplasmosis during pregnancy was unknown. Whether the screening for toxoplasmosis infection should be included in routine pre-natal examination should be evaluated carefully based on the disease incidence, the sensitivity and standardization of screening tools, the cost-effectiveness, the availability of resources, and the acceptance of general population. It is reasonable to conduct a pioneer study in some hospitals to help making a comprehensive policy.

Conclusion

Toxoplasmosis is a zoonotic disease caused by parasitic protozoa, which may result in severe illness in congenital infections and in immune compromised hosts. Considering the possible medical and paramedical expenditure, education to general population and childbearing-aged women should be enforced and notification by clinicians should be encouraged. Education materials and preventive measures should be offered.

Because effective vaccines are not available, childbearing-aged women and pregnant women with higher risk of toxoplasmosis infection should consider cash TORCH examination (a test that can detect toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, and other infections). If remote infection is found, the woman does not have to worry about acute infection during pregnancy. But if the woman has never been infected, measures should be undertaken to prevent primary infection during pregnancy, including ingestion of fully cooked meat (>66°C) and repeatedly washed vegetables, avoidance of contact to soil and contaminated cat feces, and being away from pets.

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Biosafety and Biosecurity

Confirmation of Positive Specimens from Infectious Diseases and Infectious Biological Materials

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The regulation of managing infectious biological materials, or biomaterials, for laboratory biosafety in Taiwan now followed the “Regulations governing the infectious

biomaterials and specimens collection from patients of infectious diseases" [1] (referred to as the Regulation). According to the 13th clause of the Regulation, an approval from institutional biosafety committee before any transaction of infectious biomaterials is allowed, and, if the risk level of infectious biomaterials is higher than Risk group (RG) 3, a prior approval from the central authority is required.

According to the 4th clause in Communicable Disease Control Act, the term of infectious biomaterial is defined as the material that contains the infectious pathogens and/or its infectious derivatives, and has been confirmed to contain the pathogens or the derivatives. In fact, the infectious biomaterial may come from infectious disease patient that has been tested to be positive. For example, if a serum sample was confirmed to be HIV positive, the sample should be considered as an infectious biomaterial when using the serum sample for other experiments or studies. As a result, does a positive infectious disease sample belong to infectious biomaterial? Should it be reported to the authority by regulation? It usually causes confusion to clinical examiners and laboratory managers. As a matter of fact, if we consider all positive infectious disease samples as infectious biomaterials and take controlling measure on these, it is very likely to impede the diagnosis and treatment, or the timing of epidemic investigation. Hence, a sensible and reasonable balancing point should be sought between the risk control and efficient measurement.

The definition of "positive infectious disease specimen" and "infectious biomaterial" could be categorized by the testing procedure and application. First, in the examination process of infectious specimen in clinical laboratory, the specimen could be categorized into 3 stages: "infectious disease specimen", "positive infectious disease specimen", and "infectious biomaterial". "Infectious disease specimen" refers to specimen collected from patient for the purpose of diagnosis, investigation, treatment, and prevention of the disease; including blood, body fluid, secretion, and excretion. "Positive infectious disease specimen" refers to specimen that has been confirmed as positive by examination, but there are many testing methods, e.g., antigen-antibody test cannot prove that there are pathogens in the positive specimen. "Infectious biomaterial" is the specimen from positive infectious disease which examiner considers valuable for preservation and can be used in related experiments and studies in the future, with approval by the biosafety committee (or designated specific person) of the institution. Second, infectious biomaterials are mostly preserved, and used in studies or clinical applications (e.g., drug tests). After testing result of the specimen is revealed, the doctor can make diagnosis and treatment, the specimen has done its job, and basically, it should be destroyed unless the specimen was considered to have preservation or study value. As regard to the surplus positive infectious disease specimen, it should not be used for other purpose without approval even though it was still in preservation time. If there was no preservation time interval, it should be destroyed in a certain period by internal order

of the institution. If the positive specimen is valuable for other application or study, consent by biosafety committee (or designated specific person) of the organization should be obtained before considering it as an infectious biomaterial, and all procedures should follow the Regulation.

If transfer of infectious disease specimens is necessary due to the diagnosis and treatment of the patient or epidemic investigation, the instructions in “Manual of specimen collection for infectious diseases” [2] should be followed. Two categories were sorted by risk level: specimens directly collected from patients (e.g., blood, sputum, and anal swab), and colonized culture (e.g., bacterial colony). The former are at relatively low risk because they are directly collected from patient and are not been proliferated. On the contrast, the later is at relatively high risk because it is been proliferated, like colonies of *Mycobacterium tuberculosis*. Regulations governing the transfer of infectious biomaterials should be followed if transfer or transport of the culture for drug sensitivity test is planned.

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A Brief Introduction to the Regulations of BATA and Biosafety Management System in Singapore

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The Biological Agents and Toxins Act (BATA) [1] was considered and drafted in October 2005 by National Biosafety Committee and Technique Working Groups, Ministry of Health (MOH) Singapore, with assembling of the Singapore Government and industry presenters, and then was announced and implemented in early 2006. The working groups included representatives from related government agencies, research institutions, hospitals, and key industry companies.

The main element of BATA is to officially forbid the use of biological agents and toxins for non-peaceful purpose, and to forbid using, transporting, importing, and large scale producing the biological agents and toxins in the legally-restricted list without the permission of the MOH Singapore. If people would like to use biological agents and toxins that affected human health in Singapore, import, utilize, transfer, and transport for example, they should comply with the management of the decrees and follow the safety and control regulation. With the implementation of the decrees, on the one hand, the Singapore Government hopes to ensure the related organizations and units would obey the safety

management and demands while using biological agents and toxins in Singapore, on the other hand, avoid large-scale infection caused by inappropriate management and avoid lawless persons using microorganisms as weapons.

In order to allow the implementation of BATA to qualify for the international request, the MOH Singapore explained on the internet that they adopted the WHO's Laboratory Biosafety Manual, 3rd edition [2] as the operation guideline of national biosafety to replenish the shortness of BATA. The export of biological agents and toxins that was known affecting human health was not regulated by BATA, because the exporting of related items was under domination of Singapore Customs, as for importing, there was only some demands in BATA. If violating the regulation of BATA, the management measurement included: stop the use of biological agents and toxins immediately and recycle was requested, organizations or units were asked to shutdown, and people who have contacted with biological agents or toxins may need to be medically examined, treated, isolated, or even fined or imprisoned.

The full text of BATA included eight parts. Part I is regulatory preamble, mainly are regulatory subjects and terminology. Part II includes the corresponded administrative responsibility of Singapore Government and demands, and the implementation scope. In BATA regulation, the biological agents or inactivated agents and toxins were classified into 5 categories according to their biosafety features, hence, in Part III and IV, when comes to the administrative application, use, possess, punishment of massive production without permission, import, transport, and transfer of the five categories of biological agents or toxins, the measurement of concern and explanation are provided. The details of the five categories are available in the appendix of BATA [3]. Beside, bacteria such as *Brucella melitensis, Brucella suis, Burkholderia mallei, Burkholderia pseudomallei, Clostridium botulinum* in the list of first category in Part II, and viruses like Crimean-Congo haemorrhagic fever virus, Cercopithecine herpesvirus 1, Ebola virus, Guanarito virus, Hendra virus, Junin virus in the second category, and toxins mentioned in the fifth category, were considered as categories with high risk in controlling, which are highly contagious and with potential to be made into biological weapons. Hence, among the organizations or units that work with the biological agents and toxins that mentioned above, the operating environment, equipments, and design of operating space should equip with a better safety protection and management in equipments. In Part V, the obligation and responsibility of the biosafety committee, workers, and biosafety coordinators in institutions or units working with biological agents or toxins were described, at the same time, the attitude and the package requirement for the carriers of biological agents or toxins were also regulated. In Part VI, the related permission application, license, and facility verification were explained. In Part VII, while personnel of MOH Singapore implementing the check-up, search, detention among organizations or units which use biological agents or

inactivated biological agents and toxins, their power and obligation given by law were illustrated. In Part VIII, organizations or institutions that feel treated unequally during the procedure of permission application, auditing, or if asked to revoke or withdraw the license, the ways of appeal were illustrated.

As to deal with biological agents and toxins of class 1 and 2 as stated by BATA , the organizations or units should be verified by MOH-Approved facility certifier (MOH-AFC), and then provide a complete report of facility commissioning, certification, and qualification of chief manager of laboratory according to BATA regulation, then apply for registration and permission from MOH Singapore. At the request of organizations or units, the certification would be conducted by the Approved Facility Certifier, the check-list including construction and management control, safety protection for workers and emergency response. All items are followed the WHO's Laboratory Biosafety Manual, 3rd ed. and BATA special requirements [4]. There are five MOH-AFC companies approved by MOH Singapore, three from America, one from Canada, and one from Singapore, respectively [5]. These MOH-AFC companies should be re-evaluated and re-approved by the MOH Singapore every 5 years without any fee to Singapore Government. The MOH Singapore can withdraw the authorization of these companies if they can't meet the new regulations continually.

Organizations or units that have already possessed MOH-AFC certifications should received regular onsite recertification every year by AFC. Meanwhile, if the design or structure of the facilities environment were changed, the scene certification would be arranged in advanced. If in some cases that the organizations or units were not qualified to the regulations, or there were still some improvements should be done in certain period of time, instead of MOH-AFC certification, temporary certification would be given to request the corresponding corrective action. Of course, the temporary certification was given under the premise that the facilities will work safely and no major risk existed.

Finally, a permission system, called MOH Approved Training Providers (MOH-ATP) was established for biosafety training agencies by the Ministry of Health Singapore. Any qualified personnel or agency stipulated by the Ministry of Health Singapore, with concrete outlines of the course followed the announcements, can apply for a permission. Meanwhile, it does not charge for application, so if the training providers are not able to cooperate with new regulations, the MOH Singapore has the right to withdraw the permission. There is only one agency approved by MOH-ATP so far, the Asia Pacific Biosafety Association (APBA) [6], which still has to receive the re-evaluation for permission by MOH Singapore every two years.

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