Human rabies in Tianjin, China

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ABSTRACT

Background Human rabies has recently re-emerged as a significant public health threat in Tianjin, China.

Methods Using surveillance data compiled by the Tianjin Centers for Disease Control and Prevention, we describe 60 cases of human rabies reported from 2005 to 2011 in the municipality of Tianjin, China.

Results All 60 cases of human rabies resulted in death. Cases were primarily male (80%), middle aged (mean 40.6 years), and exposed to rabies in a rural setting (82%). Most exposures were associated with dog bites (93%) and no animal had a history of rabies vaccination; no cases were laboratory confirmed. Fifteen percent of patients sought medical attention for their wound, and none received a complete regimen of WHO-recommended post-exposure prophylaxis (PEP).

Conclusions These findings suggest the need for China’s public health authority to improve animal rabies surveillance and control strategies through laboratory case confirmation, more rapid response to potential exposures with provision of appropriate PEP, and education to the public and to health care providers on identifying and reducing rabies risk.

Keywords communicable diseases, epidemiology, immunization

Introduction

The World Health Organization (WHO) estimates that 55 000 rabies-related deaths occur annually in humans worldwide and that rabies remains a significant cause of morbidity and mortality in developing countries.1 China is among the nations that experience significant numbers of human rabies cases. Since the 1950s, there have been at least three major rabies epidemics in China, each comprising over 2000 cases per year,2 and the WHO reported that China experienced 5300 human deaths in 2004 due to rabies.3 Despite this, a lack of adequate case data has contributed to the relative paucity of epidemiologic studies on human rabies in China.

Studies on human rabies in China have primarily focused on the nation’s southern provinces, where most cases are seen.4,5 However, recent increases in cases have been seen in the northwest of China in the area of Tianjin. In the past 7 years, there have been 60 known cases of human rabies in Tianjin (all of which were fatal), up from zero cases in the previous 10 years. The municipality of Tianjin is in the Hebei Province, 137 km southeast of Beijing on the Bohai coast.6 Tianjin is the third most populous city in China and with Beijing, Shanghai and Chongqing is one of only four municipalities under direct control of the national government. As of 2011, the Tianjin municipal government had a population of 10.4 million registered residents6 and an estimated additional two million unregistered residents.7 Nearly 60% of the registered population of Tianjin is urban with the remainder rural.6

China’s public health system has invested heavily in the development of their National Infectious Disease Monitoring Information System (NIDMIS), a web-based, disease-reporting
On 1 January 2004, China launched NIDMIS to monitor 37 notifiable infectious diseases, including human rabies. The system has increased the completeness and timeliness of China’s communicable disease reporting, while also enhancing their national Center for Disease Control and Prevention (CDC) institutional capacity for investigation and information sharing. NIDMIS provides an improved environment for the use of surveillance data in public health agencies by generating a more detailed epidemiological profile for diseases like rabies.

All public health surveillance, control and programmatic efforts in Tianjin are conducted by the Tianjin CDC (TJCDC) and supported by staff at smaller, district Centers for Disease Control and Prevention (district CDCs), which function like the US local health departments. As an illness of significant public health concern, reporting of rabies cases to the TJCDC is mandatory within 6 to 12 h, with more time allowed for cases in rural settings. Rapid reporting of rabies cases is intended to facilitate timely provision of rabies post-exposure prophylaxis (PEP). The TJCDC follows WHO recommendations for rabies PEP, which includes cleaning for all exposures, followed by rabies immunoglobulin (RIG) (category 3 exposures only) and vaccine (category 2 and 3 exposures) (Table 1). Like other reportable diseases, records of human rabies cases are collected, maintained and analysed by the TJCDC. The incidence of human rabies peaked in Tianjin in the 1980’s that mirrored a similar trend throughout the country. The rate has subsequently fallen although there has been an increase in Tianjin cases since 2005, possibly due to resurgence in the dog population.

In this paper, we characterize the series of 60 deaths from human rabies in Tianjin, China, over a 7-year period, and describe and assess the public health actions taken following their rabies exposure. While the number of cases may seem small in terms of the global burden of rabies, this in-depth look at post-exposure disease prevention actions is a unique examination of specific issues in rabies control. This study will be useful to other regions with similar problems, but fewer infrastructure resources.

**Methods**

Human rabies cases identified for this study consisted of those reported to the TJCDC in 2005–2011 as required by the ‘Law of the People’s Republic of China on Prevention and Treatment of Infectious Diseases’. TJCDC utilized WHO-recommended epidemiological criteria for rabies [a history of appropriate animal exposure (e.g. animal bite, scratch or exposure to body fluids)] in combination with the WHO clinical case definition for categorizing rabies:

- ‘acute neurological syndrome (encephalitis) dominated by forms of hyperactivity (furious rabies) or paralytic syndromes (dumb rabies) progressing towards coma and death, usually by respiratory failure, within 7–10 days after the first symptom, if no intensive care is instituted’.

Laboratory confirmation of human rabies cases is not currently standard practice in China and no testing was completed on any human or animal samples nor were animal or human necropsies performed on any cases in this study.

The TJCDC uses WHO criteria for determining rabies exposure that include three categories of increasing exposure severity and WHO treatment recommendations for post-exposure prophylaxis (PEP) (Table 1). WHO recommends wound cleaning as soon as possible after the exposure consisting of washing and flushing with soap and water or water alone, and disinfecting the wound with ethanol (700 ml/l) or iodine (tincture or aqueous solution). Wound cleansing should always be performed even when an individual presents at an indeterminate time following exposure.

As a component of their public health surveillance activities, TJCDC, or district CDC communicable disease staff, conducted detailed interviews with the family and supervising clinician for each reported rabies case-patient. Interviews were completed in 2005 and 2006 using open-ended questions. A quantitative questionnaire was used in 2007 through 2011 to better standardize responses. The data from questionnaires administered in 2005–2006 were subsequently transposed to the quantitative questionnaire for the use in

<table>
<thead>
<tr>
<th>Category</th>
<th>Exposure criteria</th>
<th>Biologic recommendation</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Touching, feeding of animals or licks on intact skin</td>
<td>No exposure, therefore no treatment (if history is reliable)</td>
</tr>
<tr>
<td>II</td>
<td>Minor scratches or abrasions without bleeding or licks on broken skin and nibbling of uncovered skin</td>
<td>Use vaccine alone</td>
</tr>
<tr>
<td>III</td>
<td>Single or multiple transdermal bites, scratches or contamination of mucous membrane with saliva (i.e., licks)</td>
<td>Use immunoglobulin plus vaccine</td>
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</table>

Source: World Health Organization (9). *WHO recommends wound cleaning for all types of wounds (9).*
In this study, the questionnaire collected the patients’ demographic profile (name, age, sex, occupation and address); date and geographic locale of exposure, exposure type (bite, scratch, etc.); degree of contact using WHO categories; exposure location (head, arm, etc.); wound cleaning information (date, length of time, person performing the cleansing, method of cleaning); history of rabies vaccine and RIG receipt and any information on vaccine administration related to the most recent exposure event (vaccine type, administration setting, date, vaccine manufacturer, lot number). Information was also gathered on the patients’ clinical presentation and course; animal exposure history (type, origin, vaccination history, current health status and location of animal), and questions about anyone else involved in the animal exposure (e.g. other people bitten).

In cases where only month and year of the exposure were available, the midpoint of the month was used for any date-based information. Data were entered into Microsoft Excel 2007 (Microsoft Corporation, Redmond, Washington 2007), and were analyzed with SPSS 16.0 (SPSS Inc., Chicago, IL, 2007). Analyses included simple descriptive statistics such as case counts, means and medians.

**Results**

Sixty cases of human rabies were reported to the TJCDC from 2005 to 2011, with 3, 5, 19, 10, 11, 5 and 7 cases reported each year, respectively. Table 2 summarizes risk factors and demographic characteristics of the case patients. Among the 60 individuals reported as human rabies cases in Tianjin from 2005 to 2011, 48 (80%) cases were males. The age distribution of the cases ranged from 3 years to 73 years, with a mean age of 40.6 years (median 42.5 years). Two patients were under age 16 and two were over age 60. Limited occupational data were available for 98% (59 of 60) of the cases. The majority of cases were either farmers (38%) or workers (33%) (primarily factory workers), and 27% were classified as ‘other occupation’, without a more specific designation recorded. Figure 1 illustrates the case counts by district of residence during the 7-year study period. In 92% of the cases, the exposure occurred in the district of residence, while the remainder occurred in an adjacent district or neighboring province.

Ten (17%) exposures occurred in one of the six, highly urban, city center districts, while 49 (82%) exposures occurred in more rural districts. Fifty-seven cases had exposure-type information available; 53 (88%) were exposed via an animal bite. The principle wound occurred on the hand (62%), lower leg (12%), arm (10%), head (8%), thigh (3%) or body (2%) with few unknown (3%). Based on WHO categories of exposure (Table 1), 18 (30%) of the cases were classified as category II exposures, 39 (65%) of cases were classified as a category III exposure (9) and 3 (5%) had no specified exposure category.

The animal vector for 93% of cases (56 of 60) was a dog, a cat in a two cases and two were unknown. In the 53 cases with animal origin available, 41% of the animals were identified as strays and 52% were identified as pets (among pets, 69% belonged to the patient and 31% belonged to a neighbor). Among the 36 cases where animal vaccination history was recorded, none had received rabies vaccination. Nineteen cases had information regarding the context of the attack, and in 62% of those cases, the attack was classified as ‘provoked’ or occurred while ‘playing’ with the animal.
Fifty-six patients had complete data for the incubation period (i.e. time between exposure and symptom onset) ranging from 10 to 507 days (mean = 94.3 days; median = 61.0 days). The time from the onset of clinical symptoms to death ranged from 0 to 13 days (mean = 3.6 days; median = 3.0 days). The clinical course of disease was highly variable across cases. Among all 60 cases, the most common clinical symptoms were hydrophobia (93%) and aerophobia (84%). Cases also demonstrated fidgeting (78%), photophobia (40%), tics (40%) and mental status changes (38%).

Table 3 summarizes the PEP measures (i.e. wound cleaning, administration of RIG and/or vaccine) that were provided to each patient in this series. Twenty-six (43%) patients had no wound cleaning, 23 (38%) patients cleaned the wound themselves and 9 (15%) had the wound cleaned at the hospital. Of the 39 cases with category 3 exposures, only a single patient received RIG (which was the only documented RIG administration amongst all 60 cases). This same patient also received three doses of vaccine, but died before the full five doses course of vaccine could be
completed. A total of eight patients received vaccine post-exposure (five were category III cases and three were category II cases). Five of the post-exposure vaccine recipients started vaccine on the day of the exposure; dates were missing for the other three recipients. Six of the eight vaccine recipients, including the aforementioned patient receiving vaccine and RIG, died before the five dose series was completed. The two other recipients died within a month of completing the vaccine series. A total of 26 cases (43%) did not receive any form of PEP.

**Discussion**

**Main finding of this study**

A review of 60 cases of human rabies reported in Tianjin over a 7-year period revealed that none received the full WHO-recommended PEP. Only a single case with a severe category III exposure was documented as receiving wound cleansing, RIG and vaccination, although the vaccination series was not completed. Nearly half of all cases did not have any post-exposure wound cleaning at a medical facility. This is particularly concerning as previous studies have found that local wound cleaning alone decreases the likelihood of developing rabies. This also indicates that educational efforts regarding the importance of wound cleaning need to be directed at the public and medical providers alike.

**What is already known on this topic**

The case-fatality rate of rabies is nearly 100%. Fortunately, if appropriate PEP is provisioned before symptoms develop, it is almost always preventable. The WHO recommends that all category II and III exposures receive the rabies vaccine series promptly, and category III cases should also receive RIG. It is noteworthy that of the five cases with exposures to the head (the most severe exposures), only three were known to have received vaccine; two received vaccine only, one received vaccine and RIG and two neither vaccine nor RIG. Consistent with the clinical picture of rabies, those with head wounds had the shortest incubation periods and the most rapid progression to death. Although the few patients who received vaccination had therapy initiated promptly following exposure, most died prior to administration of the complete vaccine series and the two patients who received the entire series did not receive RIG as recommended.

The reasons that patients with known rabies exposures did not receive recommended PEP were not investigated in this study, but could relate to a combination of factors; delays in care-seeking post exposure, clinicians lack of knowledge about PEP, inadequate access to clinical facilities for therapy, limited availability of immunobiologics, or possibly the prohibitive costs associated with these. All of these explanations call for somewhat different corrective actions, but clearly outreach efforts to (i) educate the public on the need to be rapidly evaluated following a possible rabies exposure, (ii) educate health care providers to identify potential exposures to rabies and provide wound cleansing and PEP and (iii) impress upon both groups the value of simple wound cleansing could be important early steps.

**What this study adds**

Similar to previous studies that examined human rabies in China, our study found that males were more frequently infected than females; likely this is related to occupational or behavioral factors that place them in greater contact with the animal vector. Unlike other studies that have found children predominantly at risk for human rabies, only four cases among our study population were less than 18 years of age, and only two of these was under age 16.

**Table 3** Details of rabies PEP in Tianjin, China

<table>
<thead>
<tr>
<th>PEP type</th>
<th>Details</th>
<th>Count</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabies immunoglobulin (RIG)</td>
<td>No</td>
<td>57</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rabies vaccine</td>
<td>None</td>
<td>52</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>2 doses</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3 doses</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4 doses</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>5 doses</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Wound cleaning</td>
<td>None</td>
<td>26</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Self</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Case-specific combinations of PEP</td>
<td>Cleaning, RIG and vaccine</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Cleaning and vaccine</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Cleaning only</td>
<td>26</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Vaccine only</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>No PEP received</td>
<td>26</td>
<td>43</td>
</tr>
</tbody>
</table>

*aFor PEP combinations, unknown or missing information was treated as ‘no’ or ‘none’. Six individuals had missing information for at least one PEP type.*
The cases of human rabies presented in this study were reported to the TJCDC via the NIDMIS. While the rapid transmission of surveillance information is important and can accelerate the epidemiological investigation of outbreaks, rabies case surveillance does little in directly preventing disease. Because clinical rabies in humans is virtually always fatal, a surveillance system that includes the report of animal exposure is essential to facilitating rabies prevention and provision of appropriate PEP, and should be implemented in Tianjin and other areas struggling to eliminate rabies.

It is likely that limited knowledge exists amongst Tianjin’s general population, and perhaps among health care providers, about rabies, its risks and specific preventive measures such as wound cleansing and PEP following animal bites. A previous study in Tianjin revealed that 81% of residents knew it was necessary to clean the wound and to obtain rabies vaccine after an animal bite, but only 21% knew the correct way to clean the wound. Furthermore, the study authors reported a rural–urban knowledge disparity, regarding the treatment of rabies, with those living in rural areas having less understanding of PEP than those living in urban areas. This knowledge disparity could help to explain our findings that the greater burden of rabies disease occurred in rural areas. Ongoing health education messages, to the general public and to clinicians, will help to address this issue.

Similar to other reports from China, in which 85–95% of human rabies cases are attributed to dog exposures, our series shows that dogs were the most common animal vector involved. Characteristics of the dog population in Tianjin are not well defined and the number of dogs is unknown. However, there is some evidence that epidemics of human rabies may be correlated with changes in the dog population. Although dog vaccination data are limited, none of the infected animals were known to have received vaccination, consistent with other studies suggesting either unknown or low animal vaccination rates. Thus, our findings re-emphasize the need for improved surveillance among the dog population, and the need for an enhanced national animal rabies vaccination program.

Laboratory tests or autopsies were neither conducted in any of the human rabies cases reported in this study nor was any animal testing performed. This is consistent with previous investigations in China and represents a common challenge in many developing countries. While some of the cases might have been incorrectly diagnosed as rabies based on clinical criteria in the presence of an appropriate exposure, it is likely that our case series represents an underestimation of the true number of cases in Tianjin. It is also possible that, inclusion of an animal exposure in the surveillance case definition could further reduce case detection sensitivity, since it is possible that individuals might not recall seemingly insignificant animal exposures that had occurred weeks or months earlier.

**Limitations of this study**

This study was subject to several limitations including small sample size, which limited our ability to perform statistical analyses on factors that predict appropriate PEP, the lack of any laboratory testing to confirm rabies in either human case patients or animal vectors, recall bias (particularly for cases that involved a long incubation period) and incomplete information from interviews about several patients. However, given the general lack of surveillance and other sources of detailed information about rabies prevention activities following exposures in developing countries, this detailed case series provides valuable information that can aid efforts to prevent rabies. This study describes many missed opportunities to prevent rabies through provision of appropriate PEP, which is likely typical in developing countries.

**Conclusion**

Through evaluation of the detailed reports on these 60 cases of human rabies identified in Tianjin between 2005 and 2011, we characterized human rabies among a population that was not previously well described. These cases clearly illustrate a need for ongoing and increased rabies surveillance among both the human and animal populations, and emphasize the importance of improved access to canine vaccination. A campaign to enhance rabies awareness for the general public should include information about rabies disease, its mode of transmission and recommendations for PEP especially among the rural population. Additionally, clinician education is crucial to increase the identification of exposures that pose a rabies risk to patients, and appropriate measures (i.e. wound cleansing and PEP) to reduce the risk of acquiring disease post exposure. Collectively, these measures could be beneficial in reducing the burden of rabies in China. Most importantly, there is definite need for improved access to and administration of appropriate rabies prevention including wound cleaning, RIG and rabies vaccine following an animal bite or other potential exposure.

**Funding**

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