Original Article

Human Rabies Epidemiology in Shandong Province, China

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(Received February 24, 2010. Accepted July 20, 2010)

SUMMARY: Rabies has reemerged in China. National rabies surveillance is centralized and based mainly on six provincial stations, including one in Shandong Province, which are selected and monitored by the China CDC. Data collection includes human rabies cases (diagnosed by local hospitals on the basis of signs or symptoms), documentation of post-exposure prophylaxis, primary laboratory diagnosis of suspect animal cases, and investigation of dog or other animal bites in viral transmission. Of the 408 human rabies cases reported during the period 2003–2007, most involved middle-aged male farmers bitten by their own unvaccinated dogs, with a seasonal peak in the autumn. These data provide key pointers regarding rabies prevention and control based upon an objective evidence-based framework.

INTRODUCTION

Rabies is an acute, progressive, and fatal zoonotic disease. Human rabies is associated with the rise of civilization, the growth of cities, and the domestication of animals, especially dogs (1). Rabies in China can be traced as far back as 556 BC in Master Zuo’s tradition of the Spring and Autumn annals (2). Although significant progress has been made in rabies control and prevention internationally, the annual human death toll, as estimated by the World Health Organization (WHO), remains at more than 55,000 worldwide (3). According to the Shandong provincial database, the German consul general in Qingdao died of rabies in 1930 (http://sd.infobase.gov.cn/bin [in Chinese]). Between 1955, when rabies was designated a reportable infectious disease in China, and 2007, a total of 5,055 human rabies cases were reported with three major epidemics in Shandong Province. The first of these outbreaks occurred between 1956 and 1958, with a peak of 803 cases in 1957, whereas the second epidemic occurred between 1978 and 1981, with 80–300 cases each year. The third outbreak occurred between 1987 and 1992, with a peak of 610 cases in 1989. Human rabies cases gradually decreased in number to zero by 1996. This general trend is consistent with the nationwide descriptions (4–6). Between 1997 and 2002, the cumulative number of human rabies cases was reported to be as low as 15, with a sporadic distribution throughout the province, whereas 14, 64, 60, 133, and 137 human rabies cases were reported in the period 2003 to 2007, respectively. To better understand the dynamics of this disease, a provincial surveillance system was established for human risk assessments.

MATERIALS AND METHODS

Data collection: Historical data concerning human rabies cases from 1956 to 2007 were obtained from the provincial reporting system. As regulated by the Surveillance Protocol in Shandong Province, any suspected human rabies case was investigated at the county or city health department level, with support from provincial Center for Disease Control and Prevention (CDC), before inclusion in the national rabies database. Information from each investigation, such as exposure description (dog or other animal bite, injury site, and severity, according to the WHO standards), patient-related information (age, gender, and address), wound cleansing, and post-exposure prophylaxis (PEP) at the local clinic, was documented. The forms and investigation report were sent to the Institute of Communicable Diseases Control and Prevention in Shandong.

Diagnostic criteria: Human rabies cases were defined according to the national WS281-2008 Rabies Diagnosis Criteria (7) and the Guidance on Rabies Prevention and Control (8). These guidelines cover the basic clinical signs of rabies and the laboratory tests used for case confirmation. Human brain samples from necropsy are rarely used to diagnose rabies in China, therefore other samples, including saliva, serum, and other secretions, were collected and sent to the provincial CDC for further laboratory diagnosis. Saliva was usually collected from the suspected rabies patient on three consecutive days.

Data analysis: Microsoft Excel and the chi-square test were used during the risk assessment. Frequency analyses were performed using the SPSS statistical package, version 10.0 (SPSS Institute, Chicago, Ill., USA).

RESULTS

A total of 5,055 human rabies cases were reported in Shandong Province between 1956 and 2007, although
only 14 of these occurred in the period 1998–2002 (mean, 2.8 cases per year). The current epidemic began in 2003, with a total of 408 cases being reported in the period 2003–2007 (mean, 81.6 cases per year), which is 29 times the total for the previous 5 years. A total of 64 cases were reported in 2004, with rabies-infected areas covering 57% (8/14) of municipal regions and 14% (20/140) of counties in the provincial jurisdiction. Similar figures were reported in 2005 (60 human cases), whereas by 2007 rabies had spread to a much larger area, with 82% (14/17) of municipal regions and 46% (64/140) of counties in the province reporting cases. All rabies cases were fatal. Figure 1 shows that the number of rabies cases in Shandong continues to rise, with 111 human rabies cases being reported in 2008.

Rabies surveillance in China is centralized at national and local levels. The fact that more rabies cases have been reported in Shandong in recent years could be a result of the reporting system established, although the main reason is the low number of dogs vaccinated against rabies. Indeed, rabid dogs were proposed to be the main source of rabies infection in the 2003 outbreak in Linyi City, although this proposal was not subsequently confirmed by a retrospective epidemiological study.

Epidemiological characteristics: (i) Geographic distribution: Although one of the 408 human rabies cases reported between 2003 and 2007 was from an unknown region, the other 407 human cases were distributed widely over 14 municipal areas, 84 counties, 322 townships, and 398 villages or communities (Table 1). Approximately half occurred in two localities, 34% (142/408) in Linyi City and 14% (57/408) in Jining City.

(ii) Seasonal distribution: Of the 408 human rabies cases studied, 55 occurred in November, 45 in October, 46 in September, 45 in August, and 41 in July. Most cases occurred in the second half of the year (259 cases, 64%), with only 63 cases (15%) in the first quarter and 86 (21%) in the second quarter (Figure 2). This seasonal peak in Shandong could be linked to the harvest season, with migrating farmers returning to town for the harvest. As can be seen from the occupational analysis, about 82% of rabies victims were farmers.

(iii) Gender and occupational distribution: The majority of the 408 human rabies cases (64%, 262/408) occurred in males, with male-to-female ratio of 1.8:1. Among the different age groups, 27% (109/408) of cases occurred in the 50–59 year age range (Figure 3). Male victims dominated all groups (Figure 4). By occupation, 82% (334/408) of cases occurred in farmers, followed by 29 cases in young students, 18 in preschool children, and a few others. Most of the infected students and preschool children came from rural areas.

Human rabies exposures: (i) Hosts: Of the 390 human rabies cases with a known history of animal exposure, 94% (366/390) were attributed to dogs, 3% (11/390) to cats, one case to an unknown wild animal, and 12 cases

Table 1. Local distribution of human rabies cases in Shandong Province, 2003–2007

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of cases</th>
<th>Municipal/city</th>
<th>County</th>
<th>Township</th>
<th>Village</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>14</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>2004</td>
<td>64</td>
<td>8</td>
<td>20</td>
<td>59</td>
<td>64</td>
</tr>
<tr>
<td>2005</td>
<td>60</td>
<td>8</td>
<td>28</td>
<td>56</td>
<td>60</td>
</tr>
<tr>
<td>2006</td>
<td>133</td>
<td>12*</td>
<td>52</td>
<td>120</td>
<td>129</td>
</tr>
<tr>
<td>2007</td>
<td>137</td>
<td>14*</td>
<td>64</td>
<td>116</td>
<td>136</td>
</tr>
<tr>
<td>Total</td>
<td>408</td>
<td>14*</td>
<td>84*</td>
<td>322*</td>
<td>398*</td>
</tr>
</tbody>
</table>

1: one with unknown origin.
2: The total with * is the cumulative, not the aggregate number.
to unrecognized hosts. Among dog bites, 54% (212/390) were produced by unleashed dogs with recognized owners. Most attacks were unprovoked, with 51% (200/390) of cases occurring as a result of the dog attacking the victim without being disturbed or teased; 42% of dogs were caught and sacrificed. A confirmatory rabies diagnosis was not performed in these animals. Records for the remaining dog bite cases were not complete. Thus, only 3% (6/212) of the dogs involved had been vaccinated against rabies. In addition, 69 (18%) dogs bit more than one person, although in each case only one person died from rabies as a result of being bitten by the same dog. Our incomplete statistics show that the dog population has increased dramatically in recent years. For example, 895,000 dogs were registered in Linyi City alone in 2005, with this number rising to 1,090,000 in 2006 and 1,716,000 in 2007. The large increase in the unvaccinated dog population is likely to be a key factor behind the increased rates of rabies infection during this period.

(ii) Exposure history: Animal exposures (bites, scratches, or both) were identified in 368 of 389 human cases (95%). According to the WHO wound exposure classification, categories I, II, and III accounted for 8, 27, and 61%, respectively, of the human rabies cases in Shandong Province in the period 2004–2007. The remaining 5% of cases were not classified due to incomplete documentation. The wounds were mostly on the hands (162/389, 42%), head (80/389, 21%), or lower extremities (71/389, 18%), and less frequently on the arms (26/389, 7%), trunk (4/389, 1%), or neck (3/389, 1%).

(iii) Prophylaxis: Approximately 56% (218/389) of the exposures received basic wound care with clean or soapy water and disinfectants. Some 34% (134/389) received one or more doses of rabies vaccine, with 34 patients who received the recommended 5 doses going on to develop rabies (Table 2). Among the category III exposures, only 7% (16/236) received human rabies immunoglobulin (HRIG). One patient received rabies pre-exposure prophylaxis, although this patient could not remember the exact time of immunization and showed no clear evidence of rabies exposure. A minor change to the wound classification system by the Chinese regulatory authorities could contribute to the increased number of patients seeking PEP. Thus, before 2003, a small wound with some bleeding was categorized as Class II, whereas after this date a minor scratch or bite from a suspected animal, without bleeding, was included as Class II exposure and PEP recommended. The high failure rate for PEP could either be due to substandard vaccine or deviation of the PEP protocol from the WHO recommendations. However, despite some news reports of counterfeit rabies vaccines, there is no solid evidence to confirm that substandard vaccines are a direct cause of PEP failure. Indeed, different vaccines, including both imported and domestically produced ones, were administered to the 134 patients (Table 2). We therefore suggest that any failure of the PEP protocol should be investigated thoroughly and independently to detect any potential errors, and that a provincial or national vaccine adverse-event reporting system should be established to track suspected problems in terms of safety and efficacy.

Clinical presentations: The median incubation period for the 375 cases between 2004 and 2007 with definite animal exposure was 53 days (Table 3). About 82% (308/375) of patients died within 6 months, and 88%
(331/375) died within a year. Most cases had typical signs or symptoms of rabies, such as anxiety, hydrophobia, aerophobia, hypersalivation, or dysphagia. The fatality rate of these cases was 100%.

**Animal rabies vaccination populations and status:** In a preliminary investigation on animal rabies vaccination in selected cities, Linyi City was found to have an average of 17 dogs and 4 cats per 100 people (estimated human population of 10,016,547 in 2007, with 1,716,323 dogs and 431,019 cats). A total of 413,987 vaccine doses were administered to dogs, 53,829 to cats, and 853 doses to other domestic animals. The estimated vaccination coverage was therefore 24% for dogs (413,987/1,716,323) and 12% for cats (53,829/431,019), assuming one dose per animal. In Linshu County, dog vaccination coverage reached 77% (74,344/96,735), whereas in Cangshan County, it was only 3% (7,890/301,760). The highest cat vaccination rate was 75% (33,349/44,661) in Linshu, with the lowest rate being 2% (300/17,800) in Yinan County. Overall, animal rabies vaccination coverage is very low in Shandong.

**DISCUSSION**

Shandong Province has a heavy burden of rabies, and the three historical rabies outbreaks reflect the discontinuous efforts in terms of dog management and mass rabies vaccination and a lack of efficient collaboration between public health, veterinary, and public authorities at all levels. When reported human rabies cases decrease below a certain level, these joint efforts cease altogether and most rabies teams at a local level are disbanded, thus resulting in periodic rabies outbreaks (6). Mass vaccination of dogs is the most efficient way to control this disease (9–11), therefore such a program should be established in Shandong for efficient rabies control.

Although the provincial CDC is responsible for collecting rabies data, it has limited access to laboratory-based diagnostic techniques, which is why not every rabies case was carefully investigated in terms of virus isolation and characterization, wound management, and PEP. Approximately 62.2% of cases in this retrospective study were associated with dog bites to the hands or head, which pose a high risk for developing rabies if no, or inappropriate, PEP is initiated (12,13). Indeed, around 42% (163/389) of category III exposures did not even receive basic wound care. Rabies awareness and education is therefore an immediate need for animal disease control and prevention. The majority of victims in the cases reported in Shandong Province were middle-aged male farmers, although the number of infections in children has grown from 7% in 2003 to 15% in 2007, thus suggesting that free-ranging unvaccinated dogs pose a major risk to those people who come into close contact with these animals.

A key finding of this study was that several patients who received PEP in clinics still died of rabies. A total of 142 patients who received PEP, including 45% (64/142) in village clinics, 28% (39/142) in town hospitals, and 10% (14/142) in county or city hospitals eventually succumbed after various incubation periods. Training qualified physicians to follow the standard PEP protocol, as recommended by WHO, appears to be vital to decrease the number of PEP failures in Shandong. Furthermore, a provincial database should be established to investigate each individual rabies PEP failure. Although rabies is fatal, it is always preventable if timely and appropriate PEP is initiated after exposure to the virus. However, a reliable diagnosis of the suspect animal is still needed in order to apply the limited vaccine and HRIG resources efficiently. Each animal bite should be carefully investigated and diagnosed in the laboratory before PEP is managed in the patient.

In summary, rabies can be controlled efficiently in Shandong, and elsewhere in China, if sufficient effort is made to ensure mass dog vaccination, basic laboratory diagnosis, and strict PEP management. These current failures arise more due to negligence by the responsible authorities than a lack of available resources.

**Acknowledgments** This study was supported by Shandong Health Department with No. 2003HZ2091.

The authors thank local Health Department employees who provided epidemiological data on these cases. The suggestions of the members of Rabies Program at the US Centers for Disease Control and Prevention (CDC) are greatly appreciated.

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