Rabies in China: recommendations for control

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Reviewed are the results of 15 years' experience with rabies at You-An Infectious Disease Hospital, Beijing, China. The purpose of the study was to determine whether there are any epidemiological or clinical features of rabies that are unique to China and which might be important in developing a strategy to control it. During the period under study, 64 patients with rabies were admitted to You-An Hospital. Exposure to dogs was associated with 61 cases, two involving the handling of dog carcasses that were being prepared for meals. All of the exposures occurred in rural areas, and none of the patients received adequate prophylaxis. Patients with proximal sites of exposure and with severe injuries developed rabies after short incubation periods (P < 0.05, and P < 0.02, respectively). Failed vaccination was also associated with a short incubation period (P < 0.05). Haematemesis occurred in 20 patients and was associated with shorter incubation periods (P < 0.02), facial exposure sites (P = 0.021), and severe injuries (P = 0.047).

A strategy to control rabies in China should include efforts to educate the public about handling the carcasses of stray dogs, in addition to the currently recommended strategy of controlling the dog population and of vaccinating domesticated animals.

Almost a century after the advent of a rabies vaccine, human rabies is a preventable disease (*1*). Despite this, human rabies is by no means rare in developing countries (*2–6*). In the present study, we review 15 years' experience of treating rabies in You-An Infectious Disease Hospital, Beijing, China. Our aim was to determine whether there are any epidemiological or clinical features of rabies that are unique to China and which might be important in developing a control strategy.

Methods

Study area

You-An Hospital (previously known as the Second Beijing Infectious Disease Hospital), a 500-bed facility that specializes in the care of patients with infectious diseases, is located in the southern periphery of Beijing. Approximately 40% of the inpatients in the hospital are residents of the municipality of Beijing (population, 10 million), 40% are from the surrounding Heibei Province, and 20% are referrals from distant areas.

Definitions and study design

The medical charts of all patients seen at You-An Hospital from 1974 to 1989 with a diagnosis of rabies were reviewed. The following case definition was used: a history of animal bite, scratch, or exposure to animal body fluids; and a clinical illness compatible with rabies, including at least three of the following symptoms: hydrophobia or aerophobia, reoccurrence of dysaesthesia or paraesthesia at the site of exposure, hypersalivation, and fever. Using these criteria, we identified 64 cases of rabies. Serological confirmation of rabies was not carried out at the hospital, nor was it standard practice to send serum specimens to reference laboratories. Also, autopsies were not performed because of family refusal in each case. However, in view of the distinct clinical syndrome presented by rabies, the strict case definition was considered to be adequate for the purposes of the study. The incubation period for rabies was defined as the interval between exposure and the onset of symptoms; the duration of illness, as the interval between the onset of symptoms and death; and fever, as a temperature of ≥38.0 °C. A dog or a cat was considered to be a stray if its owner could not be identified by either the patient or the patient's family. Exposure to rabies was taken to have occurred in a rural area if it happened outside city limits; otherwise the exposure was taken to be urban. The anatomical site of exposure was recorded, and the severity of injury was graded as follows: grade 0, no apparent injury; grade 1, skin scratched with no bleeding; grade 2, minor wound with some bleeding; and grade 3, deep or multiple wounds, or any wound requiring sutures.

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Reprint No. **5299**

Literature review

A MEDLINE literature search was conducted, with the term rabies being cross-referenced with China and with terms for gastrointestinal bleeding. The search was restricted to publications in English and to articles in other languages that had English abstracts.

Statistical analyses

Statistical analyses were performed using the χ^2 test, Student's *t*-test, and Fisher's exact test. A multivariate analysis was conducted on factors that influenced the length of the incubation period and on factors associated with upper gastrointestinal bleeding.

Results

Demographic data

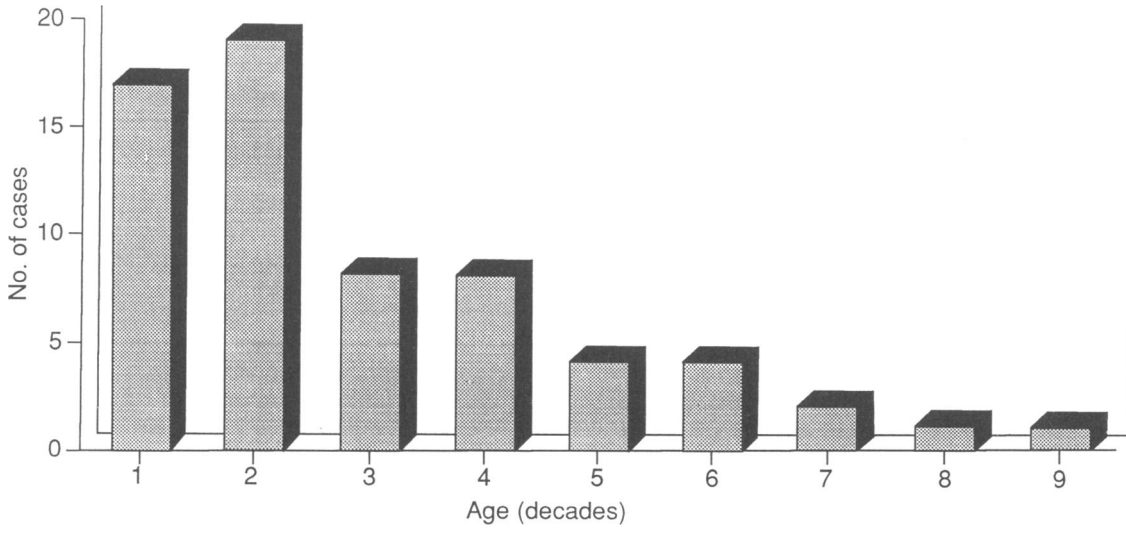
The 64 patients who met the case definition for rabies ranged in age from 2 years to 80 years (Fig. 1). Comparison of the age distribution of these patients with that for China as a whole (*7*) indicated that the two distributions were significantly different ($P = 0.02$, χ^2 test). This difference was the result of a preponderance of children with rabies, particularly among 7–12-year-olds ($P = 0.005$, χ^2 test). A total of 50 (78%) of our patients were male, compared with the Chinese sex distribution of 51.7% males and 49.3% females ($P < 0.05$, χ^2 test) (*7*).

Nature of exposure

All exposures occurred in a rural setting, and dogs were identified as the source in 61 cases. Of these dogs, 57 were domesticated, three were strays, and one was not described further. The remaining three exposures were from the bites or scratches of pet cats. In none of the cases was it known whether the offending animal had received prior rabies vaccination.

A total of 61 of the exposures were as a result of bites or scratches. Of the remaining three exposures, two were caused by handling dog carcasses being prepared for food. In one such case, the patient, on finding the family dog behaving unusually (alternately lethargic and excitable), had killed, skinned, and cooked it, and served the meat to his entire family. He was not bitten or scratched by the dog, and denied having any areas of broken skin on his hands. In the second instance, exposure resulted when a stray dog was captured and prepared for food by the patient, who had a pre-existing hand wound. The third such patient had skin contact with the saliva and urine of his rabid dog while caring for it, but denied having any open wounds at the time.

Fig. 1. **Age distribution of the 64 rabies patients in the study.**



Site and severity of exposure

The anatomical site of exposure was the head or neck in 22 cases, the hand in 28, and the lower limb in 13. Multiple site exposures occurred in five patients, in two the site of exposure was not specified, while another two had been exposed to the body fluids of sick dogs, but no portal of entry for the virus was identified. Most of the children under 10 years of age had facial bites (12 of 17), whereas most of those aged 10 years or older sustained hand bites (25 of 47 patients). The mean age of those with head or neck injuries was 16.2 ± 16.1 years, compared with 32.7 ± 19.6 years for those with hand bites ($P < 0.01$, Student's t-test).

The severity of injury was as follows: 2 patients, grade 0; 10 patients, grade 1; 31 patients, grade 2; and 21 patients, grade 3. A total of 13 of the 50 male patients had grade-3 bites, compared with 8 of the 14 females ($P = 0.038$, Fisher's exact test), indicating that although females were bitten or scratched by rabid animals less frequently than males, their injuries were frequently severe. This was explained by the higher percentage of females under 10 years of age, the group with the highest number of grade-3 bites. For this age group, the male-to-female ratio was 10:7, compared with a 7:2 overall ratio for the series. When matched for age, there was no difference in the severity of injury between the sexes. Bites on the head and neck area tended to be more severe, with 14 of the 22 such bites being grade 3; in contrast, only 6 of the 28 hand bites were grade 3. Of the grade-2 bites, only five occurred in the head and neck region, with 16 being on the hand ($P = 0.002$, Fisher's exact test).

Post-exposure wound care

Only 7 of the 61 patients with bites or scratches received specific treatment for rabies at the time of exposure, and of these none was given the recommended regimen of vaccine in combination with immune serum (Table 1). Six of these seven patients received an average of 4.2 doses of primary hamster kidney rabies vaccine without immune serum, while the seventh was given a single dose of rabies-immune horse serum. Local wound care was administered to 18 patients, nine of whom received sutures. No wound treatment was given to 25 patients, and no data were available for 17 patients.

Incubation period

The incubation period ranged from 5 days to 3 years, with a median of 41 days, and a mean of 69.7 days. For 20 patients the incubation period was less than 30 days and for 40, less than 60 days. Three patients had incubation periods of longer than 6 months but only for one patient was it longer than 9 months. This individual had been scratched (grade-1 injury) on the ankle by a dog 3 years prior to the onset of symptoms. While long incubation periods for rabies have been described previously (*8*), the fate of the dog concerned was not known, and a more recent, forgotten exposure could not be ruled out. Information on this case was therefore excluded from the statistical analysis of the incubation data. The mean incubation periods of rabies, according to the anatomical site of exposure, are illustrated in Fig. 2.

Table 1: **Treatment received by the 61 patients immediately following exposure to rabies virus**

Treatment	No. of patients
Wound washed	9
Wound washed and sutured	9
Vaccination started	6 [a]
Immune serum administered	1 [a]
Immune serum + vaccination started	0
Other treatment	1
No treatment	25
Wound treatment not specified	17

[a] These patients also received local wound care.

Shorter incubation periods tended to occur with the more proximal sites of injury. Thus, the mean incubation period for head and neck injuries was 33.2 ± 23.1 days, compared with 63 ± 57.5 days for injuries to hands ($P < 0.05$, Student's t-test). The numbers of patients in the other anatomical groups were too small for a valid statistical analysis. A similar trend was observed between the mean incubation period and severity score (Fig. 3).

Patients with grade-3 wounds had a mean incubation period of 35.4 ± 24.8 days, compared with 58.7 ± 38.4 days for grade-2 injuries ($P < 0.02$, Student's t-test), and 82.7 ± 85.2 days for grade-1 injuries ($P < 0.05$, Student's t-test). A multivariate regression analysis to determine whether the site and severity were independently related to the period of incubation revealed that both variables were significant. The mean incubation period was shorter for the 18 patients whose wounds were cleansed at the time of injury, compared with that for the 25 that were not, but the difference was not statistically significant (Table 2); this shorter incubation period arose because the more severe injuries were more likely to have received local treatment. Whether a wound had been sutured or not did not appear to influence the incubation period when the data were controlled for the site and severity of injury; however, failed post-exposure rabies vaccination was associated with a shorter incubation period. For the six patients who received rabies vaccine, the mean incubation period

Fig. 2. **Mean incubation time of rabies, according to the site of the bite**: 1 = head and neck; 2 = arm; 3 = forearm; 4 = hand; 5 = thigh; 6 = leg; 7 = ankle or foot. Because of the sample sizes, standard deviation bars are shown only for sites 1 and 4.

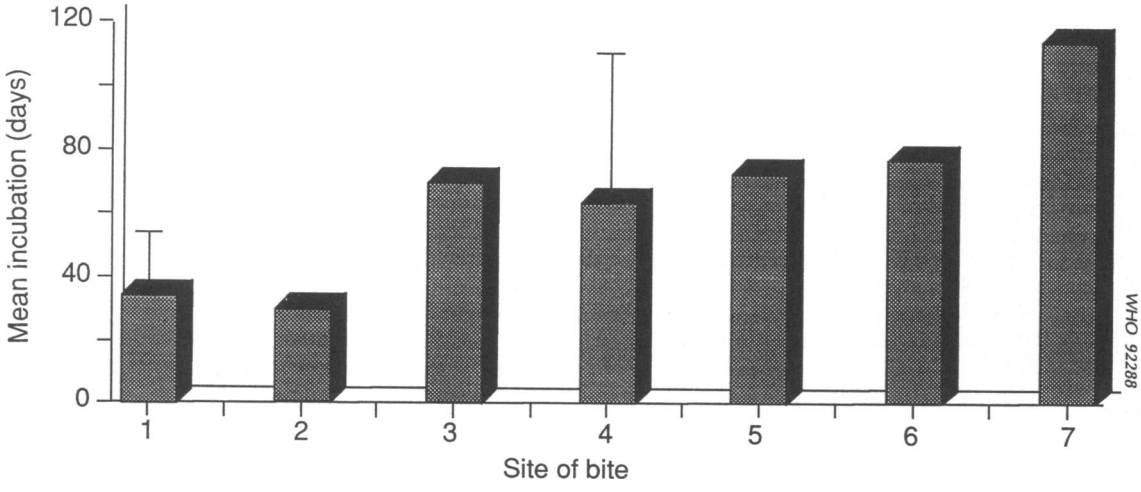
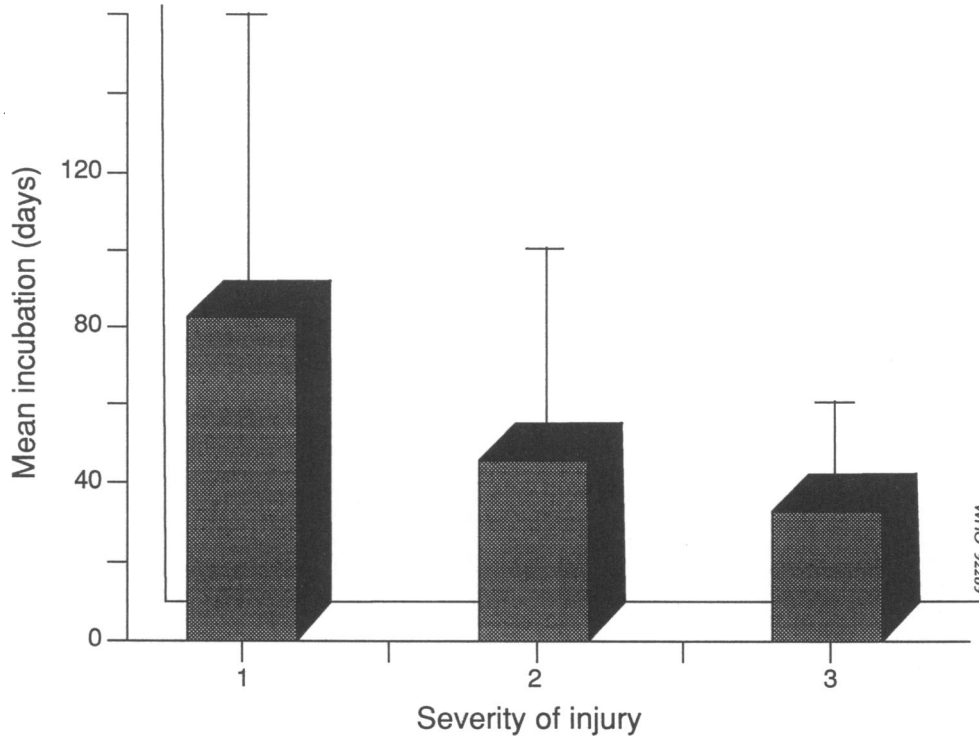


Fig. 3. **Mean incubation period for rabies, according to the severity of injury**: 1 = scratch, no bleeding; 2 = minor wound with bleeding; 3 = deep, multiple or sutured wound. Standard deviations are shown as bars.



was 22.7 ± 1.4 days. After controlling for the site and severity of the inoculated injury (grade 3, face bites), the five vaccinated patients had a mean incubation period of 18.4 ± 5.2 days, compared with 40.2 ± 21.4 days for the nine unvaccinated patients with matching injuries ($P < 0.05$, Student's t-test). These results are summarized in Table 2.

Clinical disease and outcome

Table 3 lists the frequency of symptoms used in the case definition that were manifested by the study subjects. Only two of the patients did not have either hydrophobia or aerophobia or both. Twenty patients, none of whom had received any nonsteroidal anti-inflammatory drugs, developed haematemesis as a complication of rabies. This group of patients did not differ in age, sex, duration of illness, or in the treatment they received in hospital from those who did not develop this complication (Table 4). However, patients who developed gastrointestinal haemorrhages were significantly more likely to have had the following: a short incubation period ($P < 0.02$, Student's t-test); a head or neck site of exposure ($P = 0.021$, Fisher's exact test); and a grade-3 injury ($P = 0.047$, Fisher's exact test) than those without this complication. By means of a multivariate analysis, we were unable to separate the inherent confounding effects of severity, site, and incubation period on one another in assessing their individual associations with gastrointestinal haemorrhages. Post-exposure vaccination was associated with fewer episodes of gastrointestinal bleeding when a stratified analysis was carried out using only cases with grade-3 face wounds ($P = 0.003$, Fisher's exact test). Treatment with ribavirin appeared to decrease the frequency of this complication, but the results were not statistically significant ($P = 0.055$, Fisher's exact test). These findings are summarized in Table 4. Unfortunately, the source of bleeding of these patients was not investigated.

Table 3: **Distribution of the symptoms of rabies manifested by the patients in the study**

Symptom	Present	Absent	Not documented
Hydrophobia	60	3	1
Aerophobia	61	3	0
Fever	54	8	2
Hypersalivation	40	17	7
Dysaesthesia at old injury site	15	0	49

A total of 47 of the patients died in hospital; the remaining 17 were discharged against medical advice (AMA). The two factors that influenced these AMA discharges were economical considerations (i.e., medical costs), and the rejection of "Western" medicine, with its dismal prognosis for rabies, in favour of traditional Chinese medicine. Interestingly, the proportion of such discharges decreased from 36% to 14.3% of rabies admissions after 1986 ($P < 0.001$, χ^2 test).

The mean duration of illness was 4.5 ± 2.3 days for those patients who died in hospital (range, 2–13 days). The duration of illness did not differ according to age, sex, incubation period, site, or severity of bite. Six patients received ventilatory support, which increased the mean duration of their illness to 6.5 ± 3.3 days ($P < 0.05$, Student's t-test). A total of 16 patients received intravenous doses of 16–400 mg of ribavirin, but this had no significant effect on their survival. The mean duration of illness in this group of patients was 4.0 ± 1.7 days.

Discussion

The purpose of our study was to determine whether any epidemiological or clinical features of rabies exist that are unique to China, and which might be important in developing a control strategy. A limita-

Table 2: **Influence of the post-exposure treatment on the incubation period of rabies**

	No. of patients	Mean incubation ± S.D.(days)	*P*-value
All wounds			
No treatment	25	67.2 ± 51.6	N.S. [a]
Washed	18	41.2 ± 31.5	
Grade-3 face bites			
Sutured	8	30.3 ± 24.4	N.S.
Not sutured	6	35.3 ± 9.3	
Vaccine given	5	18.4 ± 5.2	<0.05 [b]
Vaccine not given	9	40.2 ± 21.4	

[a] N.S. = not significant.
[b] Student's t-test.

Table 4: **Comparison of the characteristics of patients with and without haematemesis**

	Haematemesis		
	Present (n = 20)	Absent (n = 44)	P-value
No. of males	17 (85) [a]	33 (75)	N.S. [b]
No. who died in hospital	17 (85)	30 (68)	N.S.
Mean age (years)	24.0 ± 15.9	23.8 ± 19.6	N.S.
Mean duration of illness (days)	5.1 ± 2.6	4.2 ± 2.1	N.S.
Mean incubation (days)	34.0 ± 24.2	63.9 ± 50.2	<0.02 [c]
No. with head or neck exposure	11 (55)	11 (25)	0.021 [d]
No. with grade-3 wounds	10 (50)	11 (25)	0.047 [d]
No. in subgroup with grade-3 wounds + head or neck exposure	8	6	
No. in this subgroup vaccinated post-exposure	0	5	0.003 [d]
No. ventilated	2	4	N.S.
No. given ribavirin	2	14	0.055 [d]

[a] Figures in parentheses are percentages.
[b] N.S. = not significant.
[c] Student's t-test.
[d] Fisher's exact test.

tion that was imposed was the absence of laboratory confirmation of rabies, since no serological, immunofluorescent, or pathological diagnoses were carried out on any of the patients at You-An Hospital. This state of affairs is not unique, since in most developing countries financial, technical, and cultural barriers preclude the use of such tests in all health facilities other than a few research and treatment centres. Therefore, the majority of cases of human rabies reported to national and international health agencies are based on a syndromic diagnosis, using criteria similar to those used in this study. Furious rabies is a distinct clinical illness unlike any other, and our case definition would probably not confuse any other disease with rabies. The characteristic demographic distribution of rabies in our series (children and males being at higher risk for contracting the disease), the shorter incubation period resulting from proximal and more severe injuries, and the clinical outcome are all characteristic of rabies, and validate our case definition. Nevertheless, we probably underestimated the number of cases since approximately 20% of cases are "dumb" rabies, characterized by ascending paralysis and the absence of the classic symptoms of furious rabies.

As in other developing countries, dogs were the vectors of rabies in the vast majority of cases. Two of our cases were unique in that apparently rabid animals were killed, cooked, and eaten by the victims. In both these cases the possibility of an oral route of infection exists, as has been documented in animals (*9*). However, the rabies virus is thermolabile, and the usual mode of preparing dog meat is by cooking it thoroughly. In addition, both these patients presented with numbness and pain in their hands, a characteristic feature of rabies, where up to two-thirds of victims experience a prodromal dysaesthesia at the site of virus entry. Finally, no one else who ate the meals concerned was reported to have developed rabies. Transmission of rabies through contact with the meat of an infected animal has been described (*10*), and deserves particular attention in developing a strategy for rabies control in China, in view of the use of dogs as an edible meat source.

All of the cases in our series were from rural areas. This probably arose because most municipalities in China prohibit dogs in cities and public places, while in rural areas rabies vaccine and immune serum are scarce (*11*).

There are also indications that the incidence of rabies is increasing in China (*11*). While neither national figures nor those from the Beijing Health Bureau were available, Shandong Province reported 80 cases of rabies during the first quarter of 1989, twice the number for the same period in the previous year. In 1988, 539 deaths from rabies and 267 000 incidents involving dog bites were recorded in Shandong. The estimated dog population in the province is 6 million, with most of these dogs living in rural and unregulated areas.

Primary hamster kidney vaccine and equine immune-serum have been used for post-exposure

rabies prophylaxis in China since 1981 (*12, 13*). There is controversy as to whether the incubation period of rabies is shorter following unsuccessful post-exposure prophylaxis (*14, 15*). In our study, those patients who received post-exposure prophylaxis certainly had a shorter incubation period. In animal models a low level of antibody against rabies virus has been associated with an earlier death compared with animals with no such antibodies. This could occur also in humans. However, there is an alternative explanation: since a period of time must elapse before vaccination evokes an immune response, patients with factors that favour a long incubation period for rabies have a better chance of escaping the clinical disease (and death) than those with short incubation periods. Thus, among a group of patients given post-exposure rabies vaccine, a disproportionately large number who developed the disease would have shorter incubation periods, making it appear, spuriously, that vaccine failure hastens the disease process. In particular, this might be true when rabies immune-serum is not included as part of the prophylaxis regimen.

While gastrointestinal bleeding is a known complication of rabies, most reports of this condition are based on individual case histories, which preclude further study (*16, 18*). The present article represents the largest series of rabies patients with this complication, and we have described previously unreported correlations with gastrointestinal bleeding, i.e., severe bites, head and neck bites, and short incubation periods. However, in the absence of investigations on the reasons for the bleeding, the causative factors behind these apparent associations remain speculative.

Rabies continues to be a problem in China, despite the introduction of a safe and efficacious tissue culture vaccine in 1981. None of the cases investigated in the study received appropriate post-exposure prophylaxis for rabies, although it was initiated for six patients and then discontinued. This may have been related to the availability of vaccine, cost of treatment, or the state of public awareness about the disease. In addition, none of the animals involved was known to have been vaccinated.

Our findings permit the following conclusions to be drawn about rabies in China:

— the condition occurs primarily in rural areas after exposure to infected dogs;

— vaccine and immune serum are either not available in rural areas or are improperly used;

— transmission by handling dog carcasses deserves particular attention in rabies control in view of the role of dogs as livestock; and

— the clinical features of the disease are similar to those reported elsewhere, with the exception of a high incidence of gastrointestinal bleeding (several factors associated with this complication were identified, but their exact role remains unclear).

Application of the principles of rabies control that have been successful in other areas permit us to make the following recommendations for China.

- All domesticated animals should be vaccinated.
- All stray dogs and cats should be destroyed.
- Dog carcasses should be handled properly, with strict body fluid precautions, especially for any dog that is sick or whose vaccination status is not known—such animals should not be eaten.
- Affordable rabies vaccine and immune serum should be deployed in key locations in rural areas, so that they can be accessed and administered within 24–48 hours.
- Public education efforts should be undertaken to ensure cooperation with these control measures. (In view of the controlled production unit system of commune farms, it should be easier to implement rabies education and risk awareness programmes in these units than is generally the case in the rural areas of noncommunist countries).

Acknowledgements

This study was supported by a grant from the Canadian International Development Agency (CIDA), project number 908–282/14218, under the Canada/China University Linkage Program.

We thank Dr Roland Brant for his assistance with the statistical analysis.

Résumé

La rage en Chine: recommandations concernant la lutte

Un siècle après la découverte du vaccin antirabique, la rage humaine est une maladie évitable. Pourtant, elle n'est pas rare dans les pays en développement. Afin de déterminer s'il existe des aspects épidémiologiques ou cliniques de cette maladie qui soient uniques à la Chine, et qui pourraient jouer un rôle dans l'élaboration d'une stratégie de lutte, nous avons examiné les cas de rage survenus en 15 ans (1974–1989) au You-An Infectious Disease Hospital, Beijing, Chine. A partir des antécédents d'exposition et des critères cliniques consignés dans les registres de l'hôpital, nous avons identifié 64 cas de rage humaine. L'aspect démographique et le tableau clinique de ces cas étaient analogues à ceux observés dans

d'autres pays. Dans 61 cas, l'animal incriminé était un chien. Toutefois, dans 2 cas, la maladie a été transmise par manipulation de carcasses de chiens lors de leur préparation en vue de la consommation humaine. Toutes les expositions à la rage ont eu lieu en zone rurale. La rage frappait principalement les enfants des deux sexes âgés de 7 à 12 ans (P = 0,005) et les adultes de sexe masculin (P <0,05). Les enfants étaient surtout mordus à la tête et au cou et les adultes aux mains (P <0,01). Aucun de ces cas n'a reçu de traitement antirabique approprié. Six cas, qui ont reçu une seule dose de vaccin antirabique après l'exposition, ont eu une période d'incubation plus courte que les autres, même compte tenu du site et de la gravité de la blessure (P <0,05). La période d'incubation était également plus courte chez les sujets ayant été mordus à la tête ou au cou (P <0,05) et chez ceux ayant subi les morsures les plus graves (P <0,02). Dans cette série de cas, une complication de la rage survenait fréquemment, à savoir une hémorragie gastro-intestinale, observée dans 20 cas. Ces cas ne différaient des autres ni par l'âge, ni par le sexe, ni par la durée de la maladie; toutefois, ils avaient plus souvent été mordus à la tête et au cou (P = 0,021), avaient subi des morsures graves (P = 0,047), et avaient eu une période d'incubation courte (P <0,02). En suivant les principes de lutte antirabique qui se sont révélés efficaces dans d'autres pays, et en tenant compte de nos observations, nous avons formulé pour la Chine les recommandations suivantes:

— tous les animaux domestiques devraient être vaccinés;

— tous les chiens et chats errants devraient être abattus;

— les carcasses de chiens devraient être manipulées avec précaution (on prendra notamment garde au contact avec les liquides biologiques), surtout s'il s'agit de chiens qui étaient malades ou dont l'état vaccinal est inconnu (ces animaux ne devraient pas être consommés);

— des stocks de vaccin et de sérum antirabique à un prix raisonnable devraient être constitués dans des endroits clés situés en zone rurale, de façon à pouvoir être administrés en cas de besoin dans les 24 à 48 heures suivant une exposition;

— un effort d'éducation du public devrait être entrepris afin d'assurer sa coopération avec toutes ces mesures.

Etant donné le système de production en fermes communautaires qui prévaut en Chine, il devrait être plus facile de mettre en œuvre des programmes d'éducation et d'information du public que dans les régions rurales des pays non communistes.

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