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Review

Rabies Control in Japan

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SUMMARY: In 1957 Japan succeeded in eradicating rabies, which had been endemic since the 18th century, due to the registration and confinement of family dogs, the elimination of stray dogs, and the compulsory vaccination of dogs. At present, however, vaccination coverage of family dogs is far lower than the required level of 70%. The facilities that are presently able to investigate rabies are limited in number. In addition, few medical institutions keep rabies vaccine in stock or offer postexposure vaccination to travelers bitten by animals in rabies endemic areas. Moreover, rabies immunoglobulin (RIG) cannot be given to such individuals because RIG is not produced at present in Japan, nor is it authorized to be imported. To keep Japan free from any rabies deaths, an improvement in vaccination coverage among dogs and in the supply of postexposure prophylaxis is required, and the establishment of a rabies surveillance system is also considered to be essential.

1. Features of rabies

Rabies is a preventable, but incurable infectious disease caused by the rabies virus, which is an enveloped, bullet-shaped, single-stranded, and minus-sense RNA virus. The virus belongs to the genus *Lyssavirus* of the family *Rhabdoviridae* (1). Some rabies-related viruses are reported to cause clinical rabies in humans (2). Rabies is primarily a disease of animals and is regarded as the one of the most typical zoonoses. Rabies is known to have the following features.

1) Almost 100 % of patients who develop clinical rabies are destined to die, because the rabies virus causes fatal encephalomyelitis and no effective treatment has yet been developed (clinical features). 2) After initially propagating around the portal of entry, the rabies virus invades the peripheral nervous system and ascends to the central nervous system by a retrograde axoplasmic flow at a velocity of 8-20 mm per day (1). The symptoms of rabies, namely itchiness, pain and paresthesia around the healed bite wound, first appear after the virus enters the central nervous system. The incubation period of rabies is generally very long, 1-3 months in approximately 60% of all rabies patients (pathogenetic features). 3) The host animals of the rabies virus differ according to region, although almost all mammals can contract rabies. The main vectors of rabies are foxes in Europe and Canada, raccoons, skunks and bats in the United States, dogs in Asia, mongooses, jackals and dogs in Africa, and dogs and vampire bats in Latin America (1). There are two types of rabies epizootics, namely the urban type in which the rabies virus is principally transmitted among dogs, and the sylvatic type where the vectors are wildlife, such as foxes, raccoons and mongooses (epidemiological features).

Humans usually contract rabies through bite wounds from rabid animals (bite exposure) because the rabies virus is contained in the saliva of infected animals. Rabies can also be transmitted through non-bite exposure, although it rarely occurs. Airborne infections through the aerosol of infected animal brain tissue in virus laboratories (3-5) and through contaminated air in bat-inhabited caves (6) have also been reported. Non-bite rabies has also occurred in recipients of corneal transplantation from undiagnosed rabies patients (7-11), and after a butcher skinned a calf that died of undiagnosed neurological disease (12).

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2. Epidemic of rabies in Japan

It is said that rabies was described in the "Ishinpo", the oldest Japanese medical textbook written in 982 by Yasuyori Tanba (911-995) based on Chinese medical books of the time (13). It is uncertain, however, whether rabies occurred among dogs in those days in Japan. We tend to think that small outbreaks, originating from dogs imported from China and Korea, may have occurred sporadically.

A documented large epizootic of rabies occurred in the 18th century in Japan during the 8th Tokugawa Shogunate. During the epizootic, many dogs, horses, foxes, raccoon dogs, etc., were sacrificed. In 1756, Genjo Noro (1692-1761), one of the medical officials of the Tokugawa Shogunate, published the first textbook on the therapy of rabies, "Kyoken-kosho-chiho" which in Japanese means medical treatment for bite wounds by rabid dogs (Fig. 1). In this book he described that the sickness would become serious after a certain period of time,

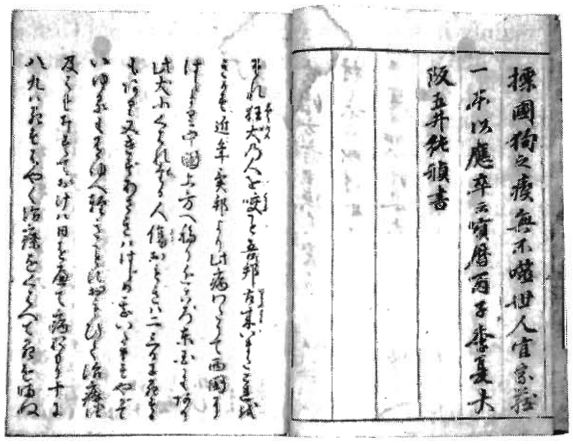

Fig. 1. Kyoken-kosho-chiho, the first Japanese textbook about the treatment of bite wounds from rabid dogs.

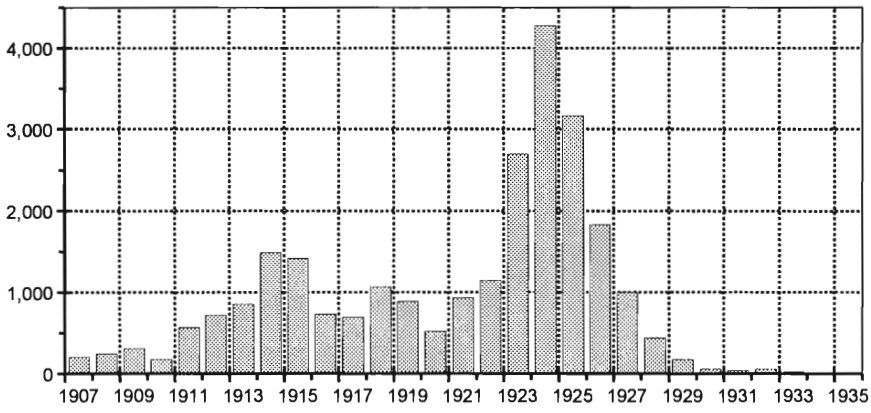

Fig. 2. Animal rabies cases reported in Japan, 1907-1935.

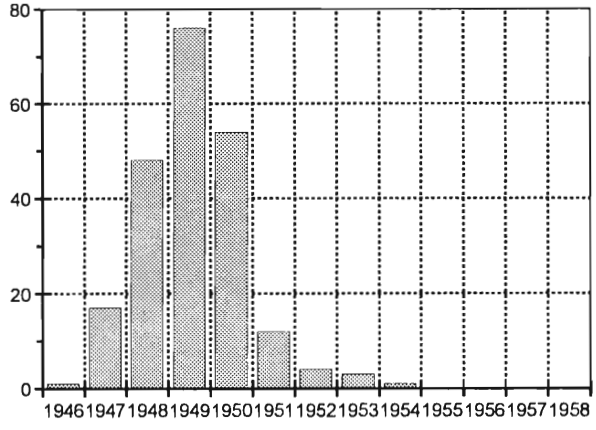

Fig. 3. Human rabies cases reported in Japan, 1946-1958.

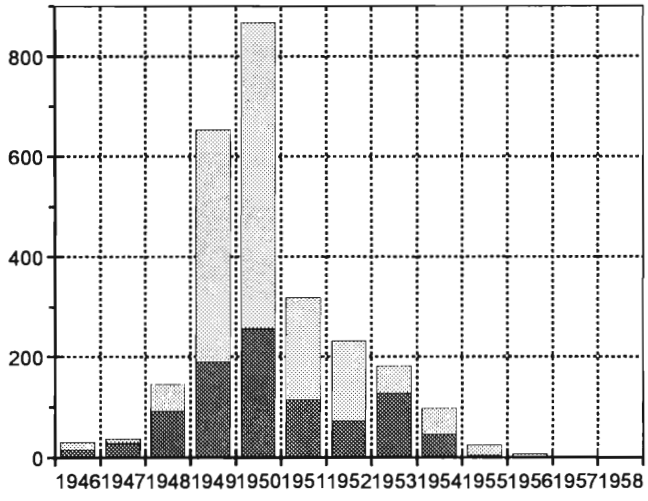

Fig. 4. Animal rabies cases reported in Tokyo (■) and in other regions of Japan (□).

even if the wounds did not appear to be severe at first, and finally 8-9 out of 10 patients would die. Furthermore, he also wrote that the best first aid treatment was to suck out the blood quickly and to apply moxa cautery to such bite wounds (14).

Little information is available on epizootics of rabies in the latter part of the Edo Era. We can only assume that outbreaks of rabies occurred sporadically in those days based on the statistics of rabid dogs during the Meiji Era (from 1868 to 1912), when 50-200 rabid dogs were recorded annually. Outbreaks of rabies gradually increased both in number and in scale in the latter part of the Meiji Era. More and more outbreaks were also reported in the Taisho Era (from 1912 to 1926), mainly in large cities such as Tokyo and Osaka. In 1924-1925, due to the confusion after the Kanto Great Earthquake (1923), the number of rabid dogs was reported to exceed 3,000 and the number of human rabies cases was over 100 per year. Thereafter, the standard rabies control methods such as compulsory vaccination of all family dogs and the elimination of stray dogs were performed all over Japan. Consequently, the number of rabid animals steadily decreased, reaching 15 or less during the period from 1934 to 1943 (13; Fig. 2).

Rabies, however, began to increase again due to the social disorder after the Second World War. In 1949, 76 cases of human rabies were reported (Fig. 3), and over 800 cases of animal rabies occurred in 1950 when the Rabies Prevention Act was enacted (Fig. 4). The Prevention Act requires owners to register and confine their dogs, and to vaccinate their dogs against rabies. This Act was strictly enforced in conjunction with the elimination of stray dogs. As a result, the number of rabid animals decreased sharply and no rabies either in animals or in humans has been reported since 1957, except for one imported human rabies case in 1970 (13).

In Japan epizootics of rabies have historically been of the urban type, with the rabies virus being transmitted from dog to dog, and occasionally from dog to humans, cats or other domestic and wild animals. During such epizootics of rabies, foxes and raccoon dogs were also infected with the rabies virus. No transmitting circle of the virus, however, was formed among the wildlife in Japan.

The elimination of rabies in Japan was thought to be possible for the following reasons: 1) The epizootics of rabies in Japan occurred principally among dogs; 2) One great advantage in preventing and to controlling animal rabies due to the fact that Japan is an island country; and 3) The Japanese people were very cooperative in vaccinating dogs against rabies and in working to eliminate stray dogs (15).

3. Actual situation of control and prevention of rabies in Japan

The control of rabies mainly depends on measures against the infection sources and transmission routes of rabies. There are two basic means of preventing people from contracting rabies, namely preexposure immunization and postexposure

prophylaxis.

3-1. Measures against the infection sources and transmission routes of rabies

Rabies control measures consist of the registration of family dogs, compulsory anti-rabies vaccination of dogs, restrictions on the movement of dogs, and the elimination of stray dogs, because no sylvatic type outbreak of rabies has occurred in Japan since the Edo Era. However, general concern about rabies in Japan is waning because neither animal rabies nor human rabies have been reported for more than 40 years in the country except for the one imported case in 1970. As a result, the number of family dogs not registered or vaccinated against rabies is increasing. In Japan, dogs had been immunized with infected animal brain-derived inactivated rabies vaccine (Semple type vaccine) twice per year from 1952 to 1984. Since 1985, a tissue-culture rabies inactivated vaccine has been obligatorily administered to dogs once a year. The positive rate of anti-rabies neutralizing antibody was reported to be 62.4% in 942 canine serum samples taken from family dogs in the City of Fukuoka during the period from 1986 to1989 (16). However, the vaccination rate and positive rate of serum anti-rabies antibody among family dogs in Japan are not known because no nationwide investigation has yet been performed. According to the announcement of the Ministry of Health and Welfare of Japan, the vaccination rate among 5.14 million registered dogs was 88.6% in 1997. The Pet Food Manufacture Association, Japan, estimates based on the results of questionnaires by interview to 6,340 randomly selected families that approximately 9.5 million dogs were kept in Japanese families. The vaccination rate would, thus, be only approximately 48%, because almost all unregistered family dogs seem not to be vaccinated against rabies. This rate is far lower than the level required to protect against an outbreak of rabies, as the World Health Organization (WHO) recommends that a 70 % immunity level should be maintained throughout the year (17). Anti-rabies vaccinations for pet cats are not obligatory in Japan.

3-2. Measures against imported animal rabies

In Japan a quarantine system is also adopted to prevent animals infected with the rabies virus from being brought into this country. Before 1998, dogs were the only animal species to be quarantined in Japan. In 1999, however, cats, foxes, and raccoons were added to the list of animals to be put in quarantine to check for rabies besides dogs. Bats have not been specified as an animal species requiring quarantine. No systems to actively survey outbreaks of rabies among domestic and wild animals have yet been established in Japan. There is no law requiring any virological investigation concerning rabies when imported animals die from uncertain cause after having passed quarantine. Moreover, even if an owner would want such examinations, it is practically impossible to perform virological or pathological investigations of dead animals, because of the limited number of facilities able to investigate rabies as well as the limited number of available staff members. In Japan, it is, therefore, practically impossible to find rabid animals and to gather virological evidence regarding rabies infection after they have settled into the country after quarantine.

3-3. Postexposure prophylaxis

Animal and human rabies still occur in many Asian countries other than Taiwan and Japan. Travelers thus need to receive postexposure prophylaxis as early as possible if they happen to be bitten by possibly rabid animals in rabies endemic regions. WHO has recommended the following postexposure treatment: the bite wound should be thoroughly washed with soap and water. Human rabies immunoglobulin (HRIG; 20 IU/kg of body weight) or equine rabies immunoglobulin (ERIG; 40 IU/kg) should be injected as much as possible around the wound and the remainder should be given intramuscularly. Next, a tissue culture-inactivated rabies vaccine should be administered on days 0, 3, 7, 14, 30, and 90 (17). Postexposure prophylaxis should be given to persons who want the treatment even months after being bitten because an incubation period of longer than 12 months has been noted in 6-7% of rabies cases (17). The vaccination schedule described above is named the Essen schedule, and it is internationally regarded as the standard method of postexposure prophylaxis.

In Japan, regarding the rabies vaccine for human use, a tissue culture-inactivated rabies vaccine is produced by a private manufacturer, the Chemo-Sero-Therapeutic Research Institute (Kaketsuken, Kumamoto) and they annually ship from 16,000-24,000 doses of their rabies vaccine (PCEC-K). The Japanese Government purchases approximately 540 doses for emergency use every two years. The PCEC-K is prepared from an attenuated rabies strain HEP-Flury grown in primary cultures of chick embryo cells concentrated and inactivated with betapropiolacton. Its antigen titer has not been officially announced. Researchers in Thailand reported PCEC-K to be less potent than rabies vaccines produced in France and Germany (18).

Neither HRIG nor ERIG are available at present in Japan, because rabies immunoglobulin (RIG) is not produced or imported. The Japanese Government has no stock of RIG. The postexposure prophylaxis according to the recommendations of WHO is, therefore, practically infeasible now in Japan.

3-4. Preexposure immunization

Preexposure immunization is recommended to persons who are living in or traveling for 3 months or longer to rabies endemic regions. WHO recommends a dose of tissue-culture rabies vaccine, with a potency of at least 2.5 IU per dose, to be given intramuscularly on days 0, 7 and 28 (17).

In Japan, whereas, preexposure immunization consists of 2 doses of PCEC-K at 30-day intervals and an additional dose at 6 months after the 2nd dose. Japanese travelers rarely plan their trips 6 months or more before their departure, except for some public employees. As a result, most travelers go to rabies endemic areas after the second dose of rabies vaccine or without any preexposure immunization.

4. Imported human rabies in Japan

One case of imported human rabies was reported in Japan in 1970. The victim was bitten by a stray dog in Nepal and developed clinical rabies after returning to Japan. In the United States, imported human rabies cases are steadily increasing, with 3 cases reported in the 1960s, 7 cases in the 1970s, and 10 cases in the 1980s (1). Eight of the 10 imported human rabies cases occurring from 1975-1984 in the United States occurred as a result of bites by rabid dogs in rabies endemic countries. Six of these 8 rabies patients had not received postexposure treatment, one had been treated too late after the exposure, while another one had been given the rabies vaccine but no RIG (19).

Recently, more and more Japanese visit various foreign

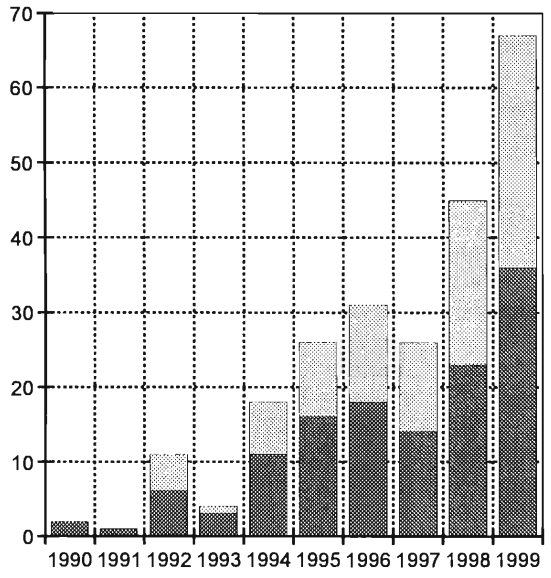

Fig. 5. Annual number of subjects (■: male, □; female) who were bitten by possibly rabid animals in the rabies endemic regions and thereafter visited our vaccine clinic to receive the rabies postexposure immunization.

countries, including rabies endemic areas. The number of Japanese overseas travelers exceeded 16 million per year in 1996. It is not rare that Japanese travelers are bitten by rabies-suspected animals in such rabies endemic regions and they do not always receive proper postexposure treatment at the place the accident occurred. The number of individuals who have been bitten by dogs, cats or monkeys in rabies endemic areas and thereafter visited our vaccine clinic to receive postexposure immunization is sharply increasing (Fig. 5). In this situation it seems rather unnatural that no imported human rabies case has been reported since 1971 in Japan.

In Japan, the domestic occurrence of human or animal rabies has not been reported for more than 40 years. As a result, there are currently few physicians who have any experience in examining rabies patients in Japan. In the United States, where only 0-6 human rabies cases have been reported annually since 1981, there have been some human rabies cases that were not suspected or diagnosed as rabies antemortem and a diagnosis of rabies was made based on pathological examinations performed postmortem (19-26). We herein cite a case report of human rabies. In this case, the diagnosis of rabies was confirmed by histological examination of brain tissue taken at autopsy (22).

Case report.

On July 5, 1993, an 11-year-old girl who lived in New York State, complained of pain in the knuckles on her left hand. The pain extended up to the left shoulder within 2 days. On July 9, she developed fever, severe muscle spasms of the left arm, difficulty walking, and hallucinations. She would not drink and had difficulty swallowing oral secretions. On July 11, she had a temperature of 40.7°C, mild meningismus, but no focal neurological findings. She was alert, oriented, and cooperative, but agitated. The patient developed respiratory distress, hypertension, tachycardia, and then arrhythmias. She died on the same day. During the autopsy performed on July 12, no brain-tissue sample was taken for viral examinations, although brain edema was noticed. About 50 days later, microscopic examination of histological slides of the brain tissue revealed possible Negri bodies. A rabies diagnosis was confirmed at the Centers for Disease Control and Prevention (CDC) in the United States. An insectivorous bat-related rabies variant virus was identified by a nucleotide-sequence analysis of the products obtained by the reverse transcriptase-polymerase chain reaction (RT-PCR) of the RNA extracted from formalin-fixed brain tissue.

In addition to the case described above, another report described a 19-year-old male in which a diagnosis of rabies was made based on a microscopic examination performed more than 2 months after the death of the patient. Rabies was ruled out in the differential diagnoses because the patient had not received any animal bite (20). Nine of 16 rabies cases that have occurred domestically in the United States since 1980 had no history of exposure to rabies (20). Rabies is often incorrectly diagnosed as encephalitis caused by other agents or as other diseases of the central nervous system in the United States due to a few human rabies cases occurring annually. In Japan, where no rabies cases have recently been reported, it is possible that rabies might be mistakenly diagnosed as another disease of the central nervous system such as Japanese encephalitis, tetanus or drug intoxication. The question as to why no imported human rabies has been reported in Japan since 1971 will not be solved as long as Japanese medical institutions fail to pay more attention to rabies and while sufficient number of virological examination facilities for rabies are not available.

5. Measures for the prevention of imported human rabies

Although rabies has essentially been eradicated in Japan, there are many countries where rabies is still endemic. The possibility that rabies may invade Japan, should therefore always be kept in mind. Recently, more than 16 million Japanese people visit abroad annually, and they increasingly prefer to visit small towns and villages alone or with a few companions instead of going in groups to famous sightseeing spots that used to be very popular among Japanese travelers. Consequently, the current risk of exposure to rabies for Japanese travelers may be much larger than that of a few decades ago. In such a situation, rabies most likely would occur among travelers who come back to Japan without proper postexposure treatment after having been bitten by stray dogs or stray cats in rabies endemic regions. We herein describe two cases of Japanese travelers who were bitten in rabies endemic areas, as follows.

Case 1. A 20-year-old Japanese female.

While traveling around in Sri Lanka, she tried to drive away a cat that had strayed into her bedroom at a hotel in the mountains and was bitten on the finger of her left hand by the cat. Bleeding from the bitten wound was noted, but she did not request medical treatment and kept traveling. Two days later, she was advised to visit a hospital by a doctor at the hotel in Colombo City. The next day she received RIG and purified Vero cell rabies vaccine (PVRV) at a hospital in the city. She was further injected with PVRV 3 days and 6 days later. After returning to Japan, she visited a university hospital near her home but they did not have any rabies vaccine available. She was, therefore, sent to our hospital and injected with PCEC-K because PVRV is not available in Japan.

Case 2. A 29-year-old Japanese male.

When he was sightseeing in rural Mexico near the United States border, he was suddenly bitten in the right lower extremity from behind by a stray dog. The teeth of the dog

bit into the bare skin of his leg and the bite wound bled. He treated the wound by himself with antiseptic solution but did not look for any postexposure treatment. Four days later he returned to Japan, and then he began to worry about rabies. He visited our clinic and received the first injection of PCEC-K 7 days after being bitten.

Almost all victims bitten by rabid animals can avoid rabies death if they receive proper postexposure treatment consisting of RIG and immunization with a tissue culture-inactivated rabies vaccine (17). Today in Japan, however, few medical institutions keep rabies vaccine in stock and thus cannot offer postexposure vaccination to travelers bitten by animals in rabies endemic areas. Moreover, RIG cannot be administered because RIG is not produced or imported at present in Japan, as mentioned above.

To receive postexposure vaccination, 45 travelers bitten by animals in foreign countries in 1998 and 67 in 1999 visited our vaccine clinic. It is reasonable to estimate, therefore, that more than 100 travelers have annually returned to Japan after receiving animal bite wounds in rabies endemic region in recent years. To prevent imported human rabies, Japanese public health authorities should ensure that a sufficient number of medical institutions can promptly provide postexposure vaccination against rabies. In addition, RIG should be immediately made available in Japan by either local production or importation.

6. Conclusions

At present in Japan, not only the general public but most medical personnel seem to have little interest in rabies, probably because no domestic occurrence of human rabies or animal rabies has been reported since 1957. Quarantine and the compulsory vaccination of dogs are both indispensable to prevent rabid animals from entering Japan and also to prevent rabies from spreading rapidly and widely if rabies were to occur domestically. Postexposure prophylaxis is essential to avoid rabies death. To keep Japan free from rabies deaths, improvements in vaccination coverage among dogs and in the supply of postexposure prophylaxis to travelers bitten by possibly rabid animals, as well as the establishment of a rabies surveillance system all over Japan are strongly called for. More than anything else, we should never forget that rabies is a preventable but incurable disease.

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