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REVIEW ARTICLE

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Rabies: a preventable but incurable disease

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Abstract Rabies is a typical zoonotic disease which has been known for more than 4300 years. To date, no effective medical therapy has been established for overt rabies. The rabies post-exposure prophylaxis (PEP), which is a serial vaccination against rabies starting as soon as possible after the patient was bitten by a suspected rabid animal, is the only way to prevent death. In Japan, no rabies case has been reported for about 50 years. However, rabies is epizootic in many Asian countries, where more than 50% of the rabies deaths in the world occur. The Japanese travelers who visit these countries every year may not be aware of this fact since no rabies occurs in their own country. Therefore, the risk of being bitten by a rabid animal abroad and developing rabies after returning to Japan seems to be high. All medical staff should keep in mind that imported rabies cases can occur at any time. In addition, pre-exposure vaccination against rabies should be recommended to international travelers in order to ensure the preventative effect of PEP.

Key words Rabies · Vaccine · Post-exposure prophylaxis · Pre-exposure immunization · Lyssavirus · Hydrophobia

Introduction

Half a century has passed since rabies was eradicated in Japan. However, in November 2006, two cases of imported rabies occurred,[1,2] reminding us that rabies is not a disease which only existed in the past. From a world-wide point of view, countries that are free from rabies are the exception, and there are still many areas in the world where rabies continues to occur.[3] However, in regions where rabies is endemic, there are some areas where many patients die from rabies, and other areas where it rarely occurs. In Asian countries, hundreds or thousands of patients are killed by rabies every year. Considering the fact that the number of Japanese people traveling to Asian countries has recently increased, imported rabies cases are much more likely to occur than an invasion of rabid animals into Japan from these areas.

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Clinical features of rabies

Rabies is mainly a disease occurring in animals, and it is regarded as one of the most typical zoonoses. Rabies is known to have the following features.

(1) The incubation period of rabies is generally very long, ranging from 1 to 3 months (about 60% of cases) to more than 1 year (6%–7% of cases) (pathogenetic features).

(2) Almost 100% of patients who develop clinical rabies die, because the rabies virus causes fatal encephalomyelitis and no effective treatment has yet been developed. There are no laboratory tests to determine whether a person is infected with the rabies virus during the incubation period (clinical features).

(3) The host animals of the rabies virus differ among regions, even though almost every mammal is capable of contracting rabies. The main vectors are foxes in Europe and Canada, raccoons, skunks, and fruit-eating and insectivorous bats in the United States, dogs in Asia, mongooses, jackals, and dogs in Africa, and dogs and vampire bats in Latin America. There are two types of epizootic rabies, namely the urban type and the sylvatic type. The former type is where the rabies virus is principally transmitted among dogs, and the latter type is where the vectors are the wildlife, such as foxes, raccoons, and mongooses (epidemiological features).

Rabies is caused by the rabies virus, which is an enveloped, bullet-shaped, size 75 nm in diameter and 100–300 nm in length, single-stranded, minus-sense RNA virus.[3,4] It belongs to the genus *Lyssavirus* of the family *Rhabdoviridae*. Genus *Lyssavirus* includes some antigenically rabies-related viruses (rabies-related lyssaviruses). Most of these

are transmitted among bats, and some are reported to cause clinical rabies in humans. Genus *Lyssavirus* containing rabies virus is phylogenetically divided into two groups, phylogroups I and II. The former includes the rabies virus, Duvenhage virus, European bat virus types 1 and 2, and Australian bat virus; the latter includes Lagos bat virus and Mokola virus.[3,5]

History of rabies in Japan

It is not known for sure when rabies appeared in human society. It is presumed that man began living with dogs about 30000 years ago, so there is a possibility that human rabies has occurred since then. The oldest document mentioning rabies as a zoonosis is the law enacted around 2300 BC in Mesopotamia.[6] The law, the Eshunna Code, imposed a penalty on the owner of the dog when a bitten victim died from rabies. From this description, it is understood that the causal relationship had been clearly recognized; the person bitten by a rabid dog would have overt rabies and eventually die. Humans and dogs were increasing in number, and people started moving to new regions with their dogs. This movement seems to be the reason why rabies spread to various regions around the world.[7]

In Japan, a large epizootic of rabies was documented in Nagasaki Prefecture in 1732, and had spread to Oita Prefecture the following year.[8] Expanding along the main roads to Sanyodo and Tokaido, it eventually reached Edo in 1736, when Yoshimune Tokugawa was governing as the 8th Shogun. During this epizootic, many dogs, horses, foxes, raccoon dogs, etc. were killed. In 1736, Genjo Noro (1692–1761), one of the medical officials of the Tokugawa Shogunate, published *Kyoken-kosho-chiho*, which is the first textbook on the therapy for rabies.[9] In this book, he reported that the sickness would become serious after a certain period of time, and eventually 8 or 9 out of every 10 patients would die, even if the wound did not initially appear to be severe. Furthermore, he also wrote that the best first-aid treatment was to suck out the blood as quickly as possible and to apply moxa cautery to the wound. This textbook was republished in 1756, probably because the epizootic of rabies had not ceased.

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 the number of rabid dogs during the Meiji Era (from 1868 to 1912), when 50–200 were recorded annually.

In 1895, an epizootic of rabies occurred in Nagasaki Prefecture. During this outbreak, Tomei Kurimoto, Chief Physician of Internal Medicine at the National Nagasaki Hospital, gave a rabies vaccination to people who were bitten by rabid dogs for the first time in Japan. He made an attenuated rabies vaccine by himself, following the method of the French scientist Louis Pasteur. He injected this vaccine into 25 patients who had been bitten by dogs, and as a result none of them died.[8]

Table 1. Numbers of rabid animals reported, regions where rabid animals occurred, and people bitten by rabid animals from 1911 to 1915 in Japan (from [10], with permission)

Year	No. of rabid animals	No. of regions	No. of people bitten
1911	570	10	904
1912	719	14	953
1913	856	18	1313
1914	1383	20	2602
1915	1424	24	3230

In the latter part of the Meiji Era, outbreaks of rabies gradually increased both in number and in scale. More and more outbreaks were reported in the Taisho Era (from 1912 to 1926), mainly in large cities (Table 1). Umeno and Doi, of the Kitasato Institute for Infectious Diseases, performed a mass rabies vaccination of dogs in Kanagawa Prefecture and Tokyo Prefecture in 1918 and 1919, respectively.[10] As a result, the numbers of both rabid dogs and people bitten by such dogs decreased significantly in both regions. However, both these numbers kept increasing outside of these regions. Owing to the widespread confusion after the great Kanto earthquake in 1923, reports of rabid dogs and human rabies cases exceeded 3000 and 100 per year, respectively, in the following 2 years. From that time, standard rabies control methods, such as compulsory vaccination of all family dogs and the elimination of stray dogs, were enforced all over Japan. Consequently, the number of rabid animals steadily decreased, reaching 15 or fewer during 1934–1943.[11–13]

However, the number began to increase again due to the social disorder after World War II. Seventy-six cases of human rabies and over 800 animal rabies cases had been reported in 1949 and 1950, respectively,[12,13] which led to the Rabies Prevention Law, enacted in 1950 (Fig. 1). This law requires owners to register, confine their dogs, and make sure that a rabies vaccination is administered. It was strictly enforced, in conjunction with the elimination of stray dogs.[13] The number of rabid animals decreased rapidly, and no rabies cases in either animals or humans have been reported since 1957, except for three cases of imported human rabies in 1970 and 2006.

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

Epidemiology of human rabies

Japan was successful in eliminating rabies, although countries free from rabies are rather an exception worldwide and there are still many endemic areas. The numbers of human rabies cases differ within these areas, ranging from areas where hundreds or thousands of people die every year to regions where human rabies is very rare. The animals trans-

mitting rabies also differ among regions, so in order to diagnose and prevent rabies it is important that we understand the epidemiology of the disease.

There are no accurate statistical data of rabies deaths in every country. The number of human rabies cases is estimated to be 55000 per year worldwide, with 56% and 44% occurring in Asia and Africa, respectively.[3] It is believed that 84% of rabies cases break out in rural and poor regions. However, the numbers of rabies deaths do not correlate with the risk of contracting rabies, because it is possible to prevent a patient from dying of rabies by giving them post-exposure prophylaxis (PEP), even after they have been bitten by a rabid animal. Without PEP, the total number of human rabies deaths in Asia and Africa combined is estimated to be about 330000.[3]

In Asia, 95% of rabies is transmitted by dogs, whereas 3% is from cats. In the United States, foxes, skunks, and racoons are the host animals. In Latin America, dogs are the host animals of rabies. In addition to terrestrial animals, some species of bat transmit rabies in North and South America. In the United States, 17 out of 19 patients who contracted rabies domestically during 2000–2006 were infected by bats.[14] In cases of bat bites, it is assumed that patients often miss out on the opportunity to receive PEP because bite wounds from bats are too small to be noticed.[15]

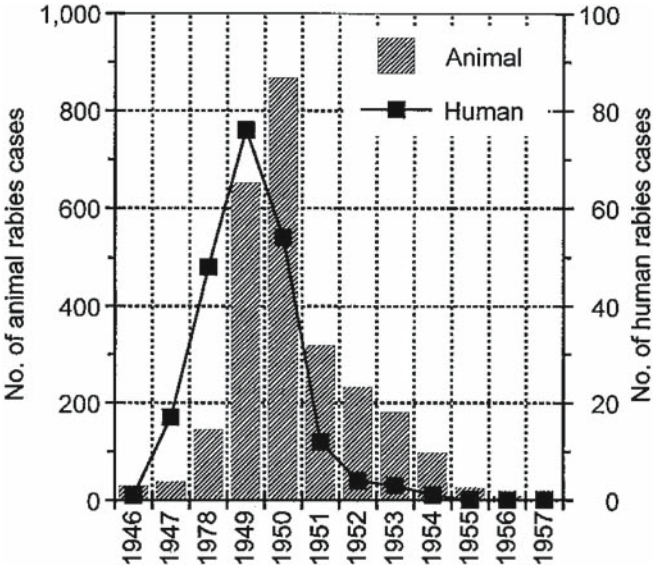

Fig. 1. Number of rabies cases reported in humans and animals in Japan after World War II. Just before World War II, the annual number of rabid animals reported was 15 or fewer because of the compulsory vaccination of family dogs and the elimination of stray dogs. However, rabies cases began to increase due to the social disorder after World War II, leading to 76 cases of human rabies in 1949 and more than 800 cases of animal rabies in 1950. In 1950, the Rabies Prevention Act was enacted. This requires dog owners to register and confine their dogs, and to vaccinate their dogs against rabies. This Act also strictly enforces the elimination of stray dogs. As a result, the number of rabid animals decreased rapidly, and no rabies case has been reported since 1957 in either humans or animals except for three imported human rabies cases. (The last human case was reported in 1954, and six rabid dogs were reported in 1956.)

Infection route of rabies

Humans usually contract rabies through bite wounds from rabid animals (bite exposure) because the rabies virus is highly concentrated in the saliva of infected animals. It can also be transmitted through nonbite exposure, although this rarely occurs. Airborne infections, such as inhaling an aerosol of infected animal brain tissue in virus laboratories, or of contaminated air in bat-inhabited caves, have been reported.[16–19] There is also one known case where a butcher became infected by skinning a cow that had died of an undiagnosed neurological disease.[20] Iatrogenic rabies cases have occurred in patients who received cornea, kidney, liver, or blood vessel graft transplantation from donors who had undiagnosed rabies (Table 2). To date, the only medically verified cases of human-to-human rabies transmission are the cases infected through organ transplantation from undiagnosed rabies patients.[21–29]

Table 2. Human rabies cases through organ transplantation

Case	Country	Year	Organ	Incubation period	Clinical diagnosis of donor	Reference number
1	USA	1979	Cornea	30 days	GBS	21
2	France	1980	Cornea	33 days	Encephalitis, myocarditis	22
3	Thailand	1981	Cornea	22 days	Not diagnosed	23
4	Thailand	1981	Cornea	31 days	Not diagnosed	23
5	India	1987	Cornea	2 days	Not described	24
6	India	1987	Cornea	257 days	Not described	24
7	Iran	1994	Cornea	26 days	Food poisoning	25
8	Iran	1994	Cornea	40 days	Food poisoning	25
9	USA	2004	Liver	20 days	SAH	26–28
10	USA	2004	Kidney	26 days	SAH	26–28
11	USA	2004	Kidney	26 days	SAH	26–28
12	USA	2004	Arterial fragment	25 days	SAH	26–28
13	Germany	2005	Lung	Not described	Not described	29
14	Germany	2005	Kidney	Not described	Not described	29
15	Germany	2005	Kiney/pancreas	Not described	Not described	29

GBS, Guillain–Barré syndrome; SAH, subarachnoid hemorrhage

Rabies through organ transplantation

In 1978, a 37-year-old American woman received a right corneal transplant from a 39-year-old lumberman who was presumed to have died from Guillain–Barre syndrome. Thirty days after the operation, she complained of right retro-orbital headache. In a few days, she noticed hypoesthesia on the right side of her face and difficulty in walking, and symptoms of dysphagia and dysarthria developed. After admission to hospital, she developed flaccid paralysis, became progressively obtunded, and eventually died on day 16 of hospitalization. A postmortem examination revealed rabies virus in the cornea, optic nerve, temporal lobe, and brain stem.[21]

In 1980, a 36-year-old man received a left corneal transplant from a 57-year-old woman who had died from encephalitis and myocarditis in France. Thirty-three days after the operation, he complained of left retro-orbital headache. Over the next 4 days he developed hypersalivation, pain and weakness in the legs, and pain on swallowing, and was hospitalized 41 days after the operation. He became comatose on day 3 of hospitalization and died on day 9. Rabies virus was isolated from the patient's brain tissue, and on histopathological examination numerous Negri bodies were found in the donor's brain.[22]

In 1981, a 41-year-old Thai woman received a corneal transplant from a boy who had died from an undiagnosed disease with mental confusion. A 25-year-old man also had a cornea transplant from the same donor. These recipients died 22 and 31 days after the operation, respectively. Rabies virus was isolated from the woman's brain tissue, and Negri bodies were found in the donor's brain tissue.[23]

In 1987, two Indian men received corneal grafts from a single donor. Nine days later, one of these recipients, a 62-year-old physician, reported redness, swelling, and intense pain in the operated eye. He died 14 days after the operation. The other recipient, a 48-year-old man, was advised to receive PEP. He received the first and second doses of rabies vaccine, but refused to take the remaining doses. He experienced dysphagia along with pain, redness, and swelling in the operated eye 257 days after the operation. Two days later, he developed hydrophobia. He died 5 days after the onset of the disease. The incubation period of the second man was more than 250 days, probably because he had received two doses of rabies vaccine.[24]

In 1994, a 40-year-old man received a corneal transplant from a 20-year-old man who had died from food poisoning in Iran. On the same day, another 35-year-old man received a cornea transplant from the same donor. The first patient reported nausea and paresthesia on his lips, and developed hydrophobia 26 days after the operation. He died within the next 24 h. The second patient was admitted to hospital with vomiting and poor general condition 40 days after the operation. He died the following day. Rabies virus was isolated from the brain tissue.[25]

In the United States, kidneys, liver, and an arterial segment were transplanted into four recipients from a common donor in 2004. All four recipients developed encephalitis within 30 days after transplantation, and died from rabies 7–23 days after the onset of neurological symptoms.[26–28]

In Germany, there was an announcement on February 16, 2005, that three out of six patients who had received organ transplantations from a common donor might have clinical rabies. The donor died after cardiac arrest and brain death in late 2004. Rabies was diagnosed in the donor and two of the recipients on the same day as the announcement and the next day, respectively.[29]

These cases indicate that organ transplants should not be carried out from donors who had died from encephalitis of unknown cause. At the same time, they also show that rabies is very difficult to diagnose intravitam.

Clinical course of human rabies

The clinical course of human rabies is divided into four phases: the incubation period, the prodromal phase, the acute neurological phase, and the coma phase.[30]

The incubation period for rabies varies from around 15 days to 1 year or even longer. In about 60% of all rabies patients, the incubation period is 1–3 months, but 6%–7% of patients exhibited an incubation period longer than 1 year. The longest incubation period reported was 7 years, and was documented for a girl who migrated from Laos to the United States.[31] She had been bitten by a stray dog in Laos 7 years before the onset of clinical rabies. In general, the incubation period is shorter when the bite is to the head rather than the extremities, and is also shorter in children than in adults. During the incubation period, the rabies virus propagates in the muscle cells around the port of entry and invades the peripheral nervous system. It then migrates centrally to the central nervous system, following the flow within the axoplasm of peripheral nerves at a velocity of 8–20 mm per day.[4] The symptoms of rabies first appear after the virus enters the central nervous system (prodromal phase).

In the prodromal phase, which lasts for 2–10 days, the patients complain of nonspecific symptoms such as malaise, fever, and anorexia. They may also complain of more specific local symptoms such as itchiness, pain, and paresthesia around the healed bite wound.

The acute neurological phase continues for 2–7 days. During this phase, patients will intermittently suffer from intense anxiety, emotional agitation, and confusion. At other times they may be calm, lucid, and cooperative toward the medical staff. About 60% of patients will develop severe pharyngeal and laryngeal muscle spasms when they attempt to drink, or even see, water (hydrophobia). Similar symptoms may also be induced when cool air blows on the face or chest (aerophobia). As a result, patients avoid drinking water, washing their hands, or feeling wind. The patient's condition gradually deteriorates. High fever, confusion, disorientation, paralysis, and general convulsions may occur, and the patient eventually falls into a coma.

In the coma phase, autonomic instability becomes extremely predominant, and hypotension, arrhythmia, and hypoventilation may develop. Most patients die shortly

after the onset of coma if no intensive supportive care is given.

No effective therapies for overt rabies have been established, so almost 100% of patients are destined to die. As of August 2007, there have been only six reports of patients recovering from overt rabies.[3]

Clinical and laboratory diagnosis of human rabies

A clinical diagnosis might be possible if the patient could describe the animal which had bitten them and in which rabies endemic area, and also if they showed typical symptoms such as hydrophobia or aerophobia. However, it is rarely possible to diagnose rabies clinically in Japan because the patient's history of animal bites is uncertain in most cases, and very few Japanese physicians have experienced clinical rabies.

An intravitam diagnosis of rabies could be made either by isolating the virus from saliva or cerebrospinal fluid, demonstrating a viral antigen in skin biopsy samples or corneal impression samples using the fluorescent antibody method, or detecting viral genes by reverse polymerase chain reaction (RT–PCR).[3,32] However, these laboratory methods are only useful after the virus has propagated into the brain tissue or disseminated to other parts of the body. They are not useful in the early stage of the disease, so it is practically impossible to diagnose rabies shortly after the onset.

Treatment of rabies patients

No medical treatment for clinical rabies has been established. Treatment is mainly aimed at minimizing the clinical signs and symptoms, and especially at reducing physical and psychological pain. Patients should be cared for in a private room with sufficient sedation. The intravenous administration of morphine is effective to relieve anxiety, agitation, hydrophobia, and aerophobia. Life-support measures should be avoided after rabies has been confirmed.[3] One case was reported of a patient who survived rabies after the use of heavy sedation in addition to antiviral medication,[33] but other clinicians were unsuccessful using the same method.[34] Before a patient is treated with these new therapies, the patient and their family should be informed of the possibility of severe neurological sequelae even if the patient did recover.[3]

Post-exposure prophylaxis (PEP)

Animal and human rabies still occurs in many Asian countries, although neither animal nor human rabies has been reported in Japan since 1957. Travelers in the endemic regions who are bitten by a possibly rabid animal need to receive PEP as early as possible. The World Health Organisation (WHO) recommends the following post-exposure treatment.[3] The bite wound should be thoroughly washed with soap and water. Next, as much human rabies immunoglobulin (HRIG, 20 IU/kg) or equine rabies immunoglobulin (ERIG, 40 IU/kg) as possible should be injected around the wound, and the remainder should be given intramuscularly. In addition, a tissue-culture-inactivated rabies vaccine should be administered on days 0, 3, 7, 14, and 30, and also on day 90 if necessary. PEP should be given to patients who request treatment even months after the bite, since an incubation period of longer than 12 months has been reported in 6%–7% of rabies cases.

The risk of contracting rabies will be higher when the patient is bitten on bare skin as opposed to through clothing, because the rabies virus is highly concentrated in the saliva. Moreover, when the face or the fingers are bitten, the incidence of rabies tends to be higher and the incubation period tends to be shorter than when the lower limbs are bitten.

Inactivated rabies vaccines marketed throughout the world are effective against lyssaviruses belonging to Phylogroup I, but are not effective against Phylogroup II.[3]

In Japan, a tissue-culture-inactivated rabies vaccine for human use (PCEC–K) is produced by a private manufacturer, the Chemo-Sero-Therapeutic Research Institute (Kaketsuken). However, neither HRIG nor ERIG is produced or imported in Japan, and furthermore, the Japanese Government has no stock of RIG. As RIG is not available in Japan, following the WHO recommendation for rabies PEP is not feasible in practice.

The PCEC-K vaccine is prepared from an attenuated rabies strain, HEP–Flury, which is grown in primary cultures of chick embryo cells. It is then inactivated with betapropiolactone, followed by concentration and purification.[35] Its antigen titer has not been officially announced. Researchers in Thailand reported that PCEC–K is less potent than rabies vaccines produced in France and Germany.[36]

PEP in our vaccine clinic

During 2000–2005, the number of patients visiting our vaccine clinic to receive PEP after being bitten by a supposed rabid animal abroad was 71–84 per year except in 2003, when the severe acute respiratory syndrome (SARS) suddenly occurred (Fig. 2). Among these patients, about 30% and 20% were between the ages of 20–24 years and 25–29 years, respectively. Eighty percent of the patients were bitten by animals in Asian countries, and in particular Thailand (40%). In detail, 81% of subjects were bitten by dogs, 11% by monkeys, and 4% by cats. About 55% of the patients attacked by animals overseas visited a local medical institute and received a rabies vaccine. The remaining 45% returned to Japan without receiving proper treatment abroad, and visited our clinic after being warned by their family members or friends of the possibility of rabies and the need for PEP.

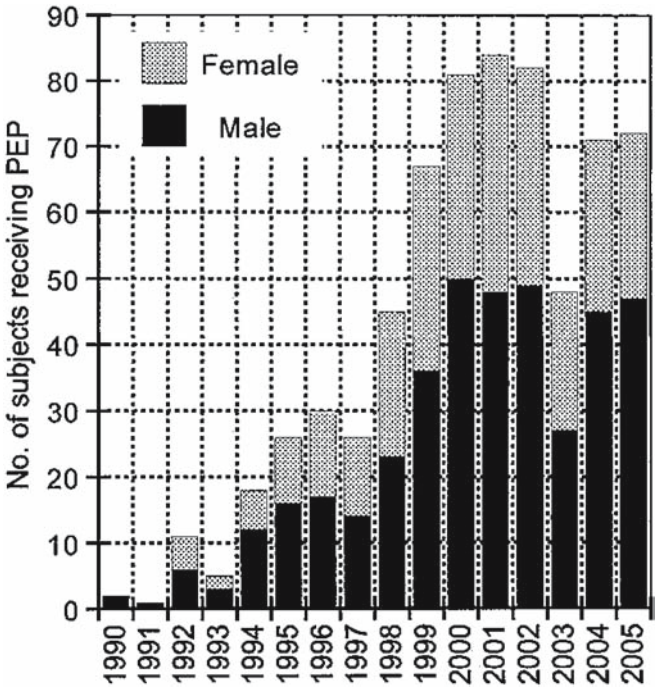

Fig. 2. The annual number of patients visiting our vaccine clinic to receive rabies post-exposure prophylaxis (PEP). The first overseas traveler bitten by a stray dog and requesting rabies PEP came to our vaccine clinic in 1990. The number of individuals receiving PEP annually in our clinic remained below 20 until 1994. However, it exceeded 20 in 1995, and continued to increase from 1997 to 2001. During this period, the annual number of Japanese people going abroad was increasing. However, we cannot explain the increase in the number of patients requesting rabies PEP simply by the rise in the number of Japanese international travelers. One speculation is that the need for rabies PEP has gradually been recognized among young Japanese adults attacked by suspected rabid animals abroad because nowadays they can easily obtain information through the Internet. On the other hand, not so many Japanese medical institutions have rabies vaccine in stock, which leads to a concentration of patients at the limited number of hospitals capable of providing rabies PEP. The decrease in the number of such patients in 2003 seems to have been caused by the outbreak of severe acute respiratory syndrome (SARS)

Imported rabies cases

In France, 19 cases of imported rabies have been reported since 1977. In England, 20 imported rabies cases were reported from 1946 to 2000. Since 2001, 2 cases have been reported in Germany, and one case each in France, England, and Taiwan.[37]

In Japan, three cases of imported rabies have been reported as of July 2007. The first case was a young adult who was bitten by a stray dog in Katmandu, Nepal, during a personal trip. About 1 month later, he complained of respiratory distress and died on the day of admission to hospital. He did not receive rabies PEP in either Nepal or Japan. Rabies was diagnosed based on the findings of a postmortem histological examination. The second and third cases were both men in their sixties.[1,2] During their long stay in the Philippines they were bitten by privately owned dogs, and they returned to Japan in November 2006 without having received rabies PEP. In both patients, the rabies virus was isolated from the saliva, and they were both diagnosed antemortem. By analyzing the gene, the rabies virus strains isolated were identified as the strain transmitted in the Philippines. In the third case, it was possible for medical staff to take the preventive measures recommended by the Center for Diseases Control and Prevention,[38] as the diagnosis was made shortly after the clinical symptoms appeared. This case was given similar treatment to the 15-year-old survival case,[31] but the treatment was unsuccessful.[1]

Pre-exposure immunization

Pre-exposure vaccination against rabies is a useful measure to prevent imported rabies. Pre-exposure immunization is recommended to people who are living in, or traveling to, high-risk regions. The 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.[3]

In Japan, pre-exposure immunization consists of two doses of PCEC–K given 30 days apart, and an additional dose given 6 months after the second dose.[35] Japanese travelers rarely plan their trip 6 months or more in advance, with the exception of some public employees. In many cases, the period available before leaving Japan is 2 months at the most. When they do not have enough time to complete the three doses, we recommend taking at least 2 doses. It is reasonably thought that patients who are bitten by a supposed rabid animal in an endemic area could efficiently produce antirabies antibody after receiving another two or three doses of the vaccine, and that they would then be protected against rabies without using RIG.

It is safer for people who are scheduled to be engaged in outdoor investigations or to handle animals to receive three doses of rabies vaccine, as recommended by the WHO, before leaving for rabies-endemic countries.

Conclusion

Half a century has passed since rabies was eradicated in Japan. However, countries free from rabies are exceptionally rare. Travel to Asian countries where many rabies victims still occur is easy, and only takes a few hours by airplane from Japan. Since Japanese travelers are rarely aware of rabies, they are at great risk of being bitten by a potentially rabid animal. Even if domestic human rabies cases no longer occur in Japan, imported rabies cases are always possible. Therefore, it is clearly important that no traveler ever carelessly puts out a hand to an animal in a rabies-endemic country. If a traveler is bitten by a suspected rabid animal in a rabies-endemic region, it is important that they receive rabies PEP in a local medical institution immediately. At the same time, pre-exposure vaccination against rabies should be recommended to international travelers in order to ensure the preventive effect of PEP. We should never forget that rabies is a preventable, but incurable, disease.

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References

1. Yamamoto S, Iwasaki C, Ohno H, Ninomiya K. Imported rabies case occurred after an interval of 36 years – Kyoto (in Japanese). IASR 2007;28:63–4.
2. Takahashi H, Sagara H, Fujita S, Hayashi H, Yoshida S, Inoue S, et al. Clinical course of the imported rabies case occurred after an interval of 36 years – Yokohama (in Japanese). IASR 2007;28: 64–5.
3. WHO expert consultation on rabies: first report. Geneva: World Health Organization; 2005. WHO Technical Report Series No. 931.
4. Fishbein DB, Robinson LE. Rabies. N Engl J Med 1993;329: 1632–8.
5. Smith JS. Molecular epidemiology. In: Jackson AC, Wunner WH, editors. Rabies. New York: Academic Press; 2002. p. 79–111.
6. Baer GM. Rabies: a historical perspective. Infect Agent Dis 1994;3:168–80.
7. Smith JS, Seidel HD. Rabies: a new look at an old disease. Prog Med Virol 1993;40:82–106.
8. Tojinbara K. History of epidemics and prevention of rabies in the dogs in Japan (in Japanese). J Jpn Soc Vet His 2002;39:14–30.
9. Noro G. Kyoken-kosho-chiho (in Japanese). Osaka: Osakashorin; 1756.
10. Umeno S, Doi Y. A study on the anti-rabic inoculation of dogs and the results of its practical application. Kitasato Arch Exp Med 1921;4:89–108.
11. Iwabuchi H. Transition in epidemic and prevention of rabies (in Japanese). Nichijukaishi 1970;23:367–76.
12. Ueki H. Tokyo–Kyokenbyo–Ryukoshi (On the epidemic of rabies in Tokyo after the World War II.) (Reprint edition) (in Japanese). Tokyo: Jikushuppan; 2007.
13. Takayama N. Rabies control in Japan. Jpn J Infect Dis 2000;53: 93–7.
14. Wyatt J. Rabies: update on a global disease. Ped Infect Dis 2007; 26:351–2.
15. Rupprecht CE, Gibbons RV. Prophylaxis against rabies. N Engl J Med 2004;351:2626–35.
16. Afsher A. A review of non-bite transmission of rabies virus infection. Br Vet J 1979;135:142–8.
17. Winkler WG, Fashinell TR, Leffingwell L, Howard P, Conomy JP. Airborne rabies transmission in a laboratory worker. JAMA 1973.
18. Conomy JP, Leibovitz A, McCombs W, Stinson J. Airborne rabies encephalitis: demonstration of rabies virus in the human central nervous system. Neurology 1977;27:67–9.
19. Constantine DG. Rabies transmission by a non-bite route. Public Health Rep 1962;77:287–9.
20. Tariq WUZ, Shafi MS, Jamal S, Ahmad A. Rabies in man handling infected calf. Lancet 1991;337:1224.
21. Houff SA, Burton RC, Wilson RW, Henson TE, London WT, Baer GM, et al. Human-to-human transmission of rabies virus by corneal transplant. N Engl J Med 1979;300:603–4.
22. Centers for Disease Control (CDC). Human-to-human transmission via a corneal transplant: France. MMWR Morb Mortal Wkly Rep. 1980;29:25–6.
23. Centers for Disease Control (CDC). Human-to-human transmission via corneal transplant: Thailand. MMWR Morb Mortal Wkly Rep. 1981;30:473–4.
24. Gode GR, Bhide NK. Two rabies deaths after corneal grafts from one donor. Lancet 1988;2:791.
25. Javadi MA, Fayaz A, Mirdehghan SA, Ainollahi B. Transmission of rabies by corneal graft. Cornea 1996;15:431–3.
26. CDC. Investigation of rabies infections in organ donor and transplant recipients: Alabama, Arkansas, Oklahoma, and Texas, 2004. MMWR 2004;53:586–9.
27. Srinivasan A, Burton EC, Kuehnert MJ, Rupprecht C, Sutler WL, Ksiazek TG, et al. Transmission of rabies virus from an organ donor to four transplant recipients. N Engl J Med 2005;352:1103–11.
28. Burton EC, Burns DK, Opatowsky MJ, El-Feky WH, Fishbach B, Melton L, et al. Rabies encephalitis: clinical, neuroradiological, and pathological findings in 4 transplant recipients. Arch Neurol 2005;62:873–82.
29. Hellenbrand W, Meyer C, Rash G, Steffens I, Ammon A. E-alert 18 February: cases of rabies in Germany following organ transplantation. Euro Surveill 2005;10:E050224.6. http://www.eurosurveillance.org/ew/2005/050224.asp#6
30. Hattwick MAW, Gregg MB. The disease in man. In: Baer GM, editor. The natural history of rabies, Vol.1. New York: Academic Press; 1975. p. 281–304.
31. Smith JS, Fishbein DB, Rupprecht CE, Clark K. Unexplained rabies in three immigrants in the United States. A virologic investigation. N Engl J Med 1991;324:205–11.
32. Trimarchi DV, Smith JS. Diagnostic evaluation. In: Jackson AC, Wunner WH, editors. Rabies. New York: Academic Press; 2002. p. 307–49.
33. Willoughby RE, Tieves KS, Hoffman GM, Ghanayem NS, Amlie-Lefond CM, Schwabe MJ, et al. Survival after treatment of rabies with induction of coma. N Engl J Med 2005;352:2508–14.
34. Hemachudha T, Sunsaneewitayankul B, Desudchit T, Suankratay C, Sittipunt C, Wacharapluesadee S, et al. Failure of therapeutic coma and ketamine for therapy of human rabies. J Neurovirol 2006;12:407–9.
35. Kondo A. New anti-rabies vaccine of tissue culture origin (in Japanese). Sogorinsho 1982;31:471–4.
36. Benjavongkulchai M, Kositprapa C, Limsuwun K, Khawplod P, Thipkong P, Chomche P, et al. An immunogenicity and efficacy study of purified chick embryo cell culture rabies vaccine manufactured in Japan. Vaccine 1997;15:1816–9.
37. Inoue S. Occurrence of rabies in the world and risk of rabies invasion into Japan (in Japanese). IASR 2005;28:204–6.
38. CDC. Rabies questions and answers. Rabies prevention and control: healthcare settings – updated May 10, 2006. http://www.cdc.gov/ncidod/dvrd/rabies/ques&ans/qa_healthcare.htm