Diagnosis, Management, and Prevention of Rabies

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Abstract

Since the Council of Agriculture reported three rabid ferret-badgers in July 2013, Taiwan has become rabies enzootic area after being rabies-free for 50 years. About 40% persons exposed to rabid animals will be infected and the mortality is extremely high. This article introduces the symptoms, diagnostic tests, management, pre-exposure and post-exposure prophylaxis of rabies. Rabies is an acute progressive encephalomyelitis. The typical clinical symptoms involve neurological presentations predominantly, including agitation, convulsion, and confusion, etc. The laboratory techniques include viral antigen detection, virus isolation, viral antibody detection, and viral ribonucleic acid detection. Due to no proven standard therapy, it is important to prevent rabies after suspect exposure to the virus, consisting of local treatment of wounds, rabies immunoglobulin (RIG) administration, and rabies vaccine injection. In response to re-emergence of rabies, Taiwan CDC has controlled and coordinated the distribution of rabies vaccines and RIG in Taiwan since July 2013. Other implemented strategies include increasing designated hospitals for rabies vaccines storage, enhancing the healthcare providers training about rabies prophylaxis.

Keyword: rabies, management, prophylaxis

Introduction

Since the Council of Agriculture, Executive Yuan identified three positive rabid ferret-badgers in July 2013, Taiwan has become rabies enzootic area after being rabies-free for 50 years. About 40% persons exposed to rabid animals will be infected and the mortality is almost 100% [1]. To facilitate the healthcare providers (HCP) to manage persons exposed to rabid animals, this article summaries the symptoms, diagnostic tests, management, pre-exposure and post-exposure prophylaxis of rabies.

Diagnosis

Rabies is an acute progressive encephalomyelitis. The clinical diagnosis is simple in a person presenting with a compatible illness (e.g. aerophobia, and hydrophobia) after documented animal exposure history [2]. In the absence of a history of exposure or paramount signs, however, the diagnosis on clinical grounds alone is difficult and laboratory testing is necessary to establish the diagnosis.

1. Clinical diagnosis

(1). Incubation: The incubation period for rabies is typically 3 - 8 weeks, but may vary from <1 week to >1 year。

(2). Prodrome:The virus moves centripetally from the periphery to dorsal root ganglia in this stage, and causes neuropathic pain at the bite site, presenting as burning, itching, pruritus. Prodromal symptoms last a few days, generally not more than a week.

(3). Acute neurological phase：Classic rabies can be classified to two forms in this phase as follows:

a. Encephalitic form: about two-thirds of patients have an encephalitic form and manifest as hyperactivity, confusion, spasm, and autonomic stimulation signs (e.g., hypersalivation, anisocoria). The spasms can be incited by tactile, auditory, visual or olfactory stimuli (aerophobia, and hydrophobia)

b. Paralytic form: the remainder present with paralysis; they generally start in the bitten limb but progress to all limbs, the bulbar and respiratory muscles. Phobic spasms may appear in only 50% of such patients and the presentations mimick other neurological disorders, such as Guillain-Barré syndrome (GBS). The following features may serve to differentiate this disorder from GBS: persistent fever from the onset of limb weakness; intact sensory function of all modalities except at the bitten region; percussion myoedema; and bladder dysfunction.

(4). Coma: The patients become comatose after 1-2 weeks of acute neurological phase and die of arrhythmia or myocarditis [2].

2. Laboratory diagnosis

The rabies diagnostic tests include viral antigen detection, virus isolation, viral antibody detection, and viral ribonucleic acid (RNA) detection (Table 1). The last two methods are available in Centers for Disease Control (CDC), Taiwan.

3. Image study

Computerized tomography of the brain is of little diagnostic value [2], but magnetic resonance imaging (MRI) when performed with adequate precautions can be helpful [13]. Typical MRI abnormalities are hypersignal T2 changes involving the spinal cord, brain-stem, thalamus, limbic system, and white matter during the non-comatose phase. During the comatose phase, widespread T2 hyperintense lesions in the forebrain can be seen. Such progressive patterns can help to differentiate rabies from other viral encephalitides [2].

Management

The mortality rate of rabies is extremely high. Due to no proven standard therapy, current management for rabies patients is mostly symptomatic and palliative [2, 3, 13], including adequate sedative agents, setting the patients in a private, quite area, and emotional support. Some therapeutic agents, such as combination therapy with immunoglobulin plus vaccination, ketamine and interferon-α, or large doses of intravenous human rabies immunoglobulin (RIG)

had been advocated with limited success [13]. There is a survived rabies patient under the treatment of the "Milwaukee protocol", developed by the Medical College of Wisconsin, consisting of supportive care, therapeutic coma, and antiviral agents. However, data about the protocol have been conflicting. In the protocol, the rabies vaccine and immunoglobulin are considered to be avoided if possible, due to slow natural immune response and may not penetrate blood-brain barrier, respectively [15]. Some researchers are concerned about clinical deterioration after receipt of rabies vaccine and immunoglobulin [16].

Table 1. Laboratory assays for rabies diagnosis

Method	Description	Advantage	Disadvantage	Sensitivity / Specificity
Antigen detection				
Direct fluorescent antibody technique, (DFA)	1. Gold standard for rabies diagnosis 2. The test is based on microscopic examination of smears of brain, skin from the nuchal area of the neck, and salivary gland biopsy samples after incubation with anti-rabies polyclonal or monoclonal antibodies.	Lower cost, rapid (2-4 hours).	* The sensitivity is influenced by the sample type, experience of the performer, and quality of the used antibodies and equipment. *It may not be practicable in decomposed tissues.	98.3% / 97.3% [7]
Enzyme-linked immunosorbent assay(ELISA)	1. Useful for large epidemiological surveys. 2. Provides results of high agreements with the DFA (96%) [8].	* Lower cost, rapid (few hours). * Practicable in decomposed tissues. * Easy to perform. * Do not need for microscopy * Suitable for large numbers of samples.	* Less sensitive than DFA, and not suitable for confirmative diagnostic test.	95.0% / 99.9%[a][8]
Antibody detection				
Rapid fluorescent focus inhibition test(RFFIT)	1. Neutralizing antibodies tend to appear on average 7-8 days after clinical symptoms, and are considered of little value as a confirmatory test. 2.Useful in the detection and quantification of rabies antibody in animals and humans post vaccination. 3. Serum is the commonly used specimen due to viral antibodies seldom found in the cerebrospinal fluid.	* Reference test to monitor neutralizing antibodies.	* Longer turnaround time (24-48 hours). * Requirement for specialized labs capable of handling live virus. * Higher cost.	74% / 98%[9]
Fluorescent antibody virus neutralization test (FAVN)		* Reference test to monitor neutralizing antibodies. * Appropriate for dealing with the large numbers of samples.	* Longer turnaround time (48 hours) * Requirement for higher cost and larger volumes of examined serum than the RIFFT * Requirement for specialized labs capable of handling live virus	88.6% / 100%[b][10]
ELISA		* Lower cost, rapid (4 hours) * Easy to perform * Do not need specified labs	*Not specific to neutralizing antibodies *Less sensitive than RIFFT	66%/ 100%[9]
Virus isolation				
Inoculation of laboratory animals	Isolation of virus following intracerebral inoculation of weaned mice with homogenized suspensions of brain, spinal cord or salivary gland from suspected rabid cases.	* Confirmation test for the samples with negative or uncertain DFA results. * Amplification of virus for further characterization of the isolate. * Useful in labs without cell culture facilities.	*4 weeks or even longer for final results (It can be shortened to 10-21 days if the suckling mice were used).	
Isolation of rabies virus in cell culture	Homogenized specimens can be inoculated directly onto monolayer cell cultures.	* Confirmation test for the samples with negative or uncertain DFA results. * Lower cost, rapid (1-2 days) when compared to animal inoculation. * Do not involve the use of live animals.	* The sensitivity varies with different cell lines used.	
Viral ribonucleic acid detection				
Reverse Transcriptase-Polymerase chain reaction (RT-PCR)	Despite not recommended if DFA available, RT-PCR is playing an increasingly important role in diagnosis, strain characterization, and epidemiological surveys.	* Useful in decomposed samples or liquid specimens, e.g., saliva, tear. * To discriminate between rabies virus and other *Lyssaviruses*. * Rapid (few hours).	* Serial samples of saliva and urine should be tested, as the virus is excreted intermittently. * The sensitivity is influenced by the sample amounts and specimen types.	8.0 – 100% / 100%[c] [11, 12]
Histopathology	Rabies virus causes encephalitis with limited cellular damage. However, Negri body, an intracytoplasmic, eosinophilic inclusion body, can be found in rabies-infected tissues.	* Easy to perform * Pathognomonic feature of Negri body.	* Low sensitivity, influenced by samples from different site. * Longer turnaround time * More expensive than DFA.	50 - 80% / 93.5%[7]

a. compared to DFA; b. compared to RIFFT; c. The sensitivity varies between different specimens

Prophylaxis

1. Post-exposure prophylaxis (PEP)

Due to no effective therapy nowadays, it is important to prevent rabies after suspect or proven exposure to the virus, including timely local treatment of wounds, passive immunization (RIG), and active immunization (rabies vaccines) [2, 17, 18]. The recommendations regarding PEP between U.S. Centers for Disease Control and Prevention and World Health Organization (WHO) are different. The Advisory Committee on Immunization Practices (ACIP) in Taiwan, following recommendations of WHO, established the guidance for PEP according to categories of exposure and types of exposing animals (Table 2, 3). The guidance will be modified timely according to surveillance data of rabid animals from the Council of Agriculture. For example, after the positive rabid house shrew identified on July 30th, 2013, which was the first trans-species infection in Taiwan, people exposed to house shrews, stray dogs and cats have become eligible to government-funded PEP.

Table 2. Recommendations for administration, brands, dosages, and adverse effects of rabies immunoglobulin (RIG)

Exposing animal species	Recommendations
1. Ferret-badger 2. House shrew (Taitung County only) 3. Animals behaving abnormally (e.g., unprovoked attack) and tested positive for rabies by the Council of Agriculture	1. Administer RIG for all persons with category III exposures 2. Administer RIG for immunocompromised cases with category II exposures or for immunocompetent cases with category II exposure to positive rabid ferret-badgers

Immunoglobulin	Human RIG	Purified equine RIG
Brand	Hyperrab	Favirab
Dose	20 IU/kg	40 IU/kg
IU/ml	150 IU/ml	200 IU/ml
Contraindication	No	History of allergy to equine protein
Adverse reactions	Soreness and mild temperature elevations may be observed at the site of injection. Sensitization to repeated injections has occurred occasionally in immunoglobulin - deficient patients. Angioneurotic edema, skin rash, nephrotic syndrome, and anaphylactic shock have rarely been reported.	Adverse effects are observed in less than 10% of subjects. The immediate reactions are anaphylactic reactions with hypotension, dyspnea, and urticaria. In rare cases (less than 1 case in 10,000), more severe reactions such as angioneurotic edema or anaphylactic shock may develop. Delayed-type reactions may occur about six days after the injection, consisting of fever, pruritus, erythema, urticaria, adenopathy, and arthralgia.

Table 3. Recommendations for rabies vaccination according to exposing animals

Animal types	Recommendations	Notes
Wild mammals (including house shrew)	Administer vaccine for categories II and III exposure	The vaccination can be discontinued if the exposing animals is tested negative for rabies
Stray dogs and cats	Administer vaccine for categories II and III exposure	The vaccination can be discontinued if the exposing animals are confined for 10 days remaining alive and healthy
Domestic dogs, and cats	Vaccination is not recommended	Administer vaccine if the exposing animals present signs suggestive of rabies during the 10 days observation period, and are confirmed positive for rabies by the official laboratory

(1).Management of wounds:

Irrigate the wounds immediately and thoroughly with running water or soap water for at least fifteen minutes, and sterilize the wounds with povidone-iodine solution. Suturing of wound should be avoided as far as possible. If surgically unavoidable, minimum loose sutures should be performed for debris discharged smoothly. If RIG has been administered, suturing should be performed several hours later (more than 2 hours) for antibodies infiltrating into tissues properly [18]. Thorough wound cleansing alone markedly reduce the likelihood of rabies in animal studies [17].

(2).Passive immunization:

RIG provides rapid immunity to tide over the initial phase after vaccination before neutralizing antibodies inducted. The ACIP in Taiwan proposes guidance for the RIG administration according to categories of exposure [2] and types of exposing animals (Table 2). The full dose of RIG, according to body weight of the cases, should be thoroughly infiltrated in the area around and into the wounds if possible. Any remaining volume should be injected into deep muscles at the wounded limb (e.g., deltoid or anterolateral thigh). If wounds were severe and multiple (most likely in children), dilute the RIG in sterile normal saline two to three fold to be able to permit infiltration of all wounds.

RIG can be administered concomitantly or up to seventh day after vaccination. However, RIG should be administered at a site distant form the site of the first vaccine dose as it may suppress the antibody production. Beyond the seventh day after vaccination, RIG is not indicated since an antibody response to vaccine is presumed to have occurred. There are two classes of RIG available in Taiwan: human rabies immunoglobulin (HRIG) and purified equine rabies immunoglobulin (pERIG), both recommended by WHO (Table 2).

(3).Active immunization:

Rabies vaccines, inducing active neutralizing anti-rabies antibodies, should be administered as soon as possible after exposure. The five-dose regimen consists of one dose each on days 0 (the date of the first dose of vaccine administration), 3, 7, 14 and 28. The vaccination should be administered in the deltoid area or the anterolateral thigh and avoid the gluteal area due to lower neutralizing antibody titers production. For previously vaccinated persons, whether complete pre-exposure (PrEP) or post-exposure prophylaxis, who are exposed to rabies, two doses of vaccine should be administered, one immediately and one 3 days later. In the “International Expert Meeting” on August 2013 [19], the experts suggested that such persons should be re-vaccinated regardless of the last vaccination date or the neutralizing antibody titer.

Because the high fatality of rabies, the benefits of the vaccination outweigh the risks in pregnancy, lactation, and infantile, and these conditions are not contraindication for vaccination [2, 17].

(4).Immunosuppression:

The immune response to vaccination in immunocompromised individuals might be inadequate and PEP recommendations for such persons are different from those for immunocompetent persons [2,17]. The definitions of immunosuppression are [18]:

a. Patients with human immunodeficiency virus infection, post-transplantation within 2 years or receiving immunosuppressive agents continuously.

b. Patients with congenital immunosuppression, asplenia, autoimmune disease under corticosteroids or other immunosuppressive agents, malignancy under chemotherapy, malaria under chloroquine treatment.

c. Patients with other medical conditions which might influence immune functions, including chronic kidney disease, diabetes, liver cirrhosis, chronic liver disease, etc.

If these persons have not received complete PrEP or PEP previously, RIG and a complete series of five intramuscular doses of rabies vaccine should be administered regardless of category II or III exposures according to the recommendations of WHO [2]. The guidance for immunocompromised individuals in Taiwan is tailored according to epidemiologic data of animal rabies, mostly similar to the guidance for the immunocompetent persons, except that RIG and a complete series of vaccination will be prescribed for immunocompromised cases with category II exposure to ferret-badgers. If these persons have received complete PrEP or PEP previously, a complete series of five doses of rabies vaccine is required and RIG is unnecessary. In capable labs with optimal resource, neutralizing antibody titers should be determined 2-4 weeks after completion of PEP (≥ 0.5 IU/mL or 1:5 serum dilution by RFFIT [2]; ELISA can be used as an alternative test [9]) for decision-making about a single booster dose of vaccine. Experts should be consulted if the titer less than the reference value. For immunocompromised individuals, intradermal vaccine injection or schedules other than five-dose regimen are inappropriate, and the PEP should be considered as incomplete.

2. Pre-exposure prophylaxis

U.S. CDC and WHO both recommend PrEP for anyone who is at continual, frequent or increased risk for exposure to the rabies virus as a result of their occupation, such as laboratory worker dealing with rabies virus, veterinarians, and wildlife workers. Three-dose regimen can be administered, one injection each on days 0, 7, and 21 or 28 [2, 17]. For the safety of animal disease control professionals, wildlife workers, stray animal-control officials, Taiwan CDC offers PrEP to these populations according to the lists provided by central departments and local county governments after risk assessment.

Table 4. Rabies pre-exposure prophylaxis guidelines - U.S. Centers for Disease Control and Prevention [18]

Risk category	Nature of risk	Typical populations	Recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.	Rabies research laboratory workers; rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below a 1: 5 serum dilution.
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.	Rabies diagnostic laboratory workers, veterinarians and staff, animal-control and wildlife worker in area where rabies is enzootic. All persons who frequently handle bats.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below a 1: 5 serum dilution.
Infrequent	Exposure nearly always episodic with source recognized.	Veterinarians and animal-control staff in areas where rabies is uncommon to rare. Veterinary students, travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care is limited.	Primary course. No serologic testing or booster vaccination.
Rare	Exposure always episodic with source recognized. Bite or nonbite exposure.	General populations.	No vaccination is necessary.

3. Establishment of vaccine supply plan

People who had been bitten by animals did not receive PEP during the past fifty years when Taiwan had been listed as rabies-free. Hence, only about 300 doses of human rabies vaccines and 10 doses of HRIG are stockpiled annually in Taiwan CDC for PEP for travelers returning from overseas area with enzootic rabies. In response to re-emergence of rabies, Taiwan CDC have controlled and coordinated the distribution of all stored rabies vaccines and RIG (including official and of manufacturers) in Taiwan since 2013 July. To implement a complete prophylaxis campaign, the other strategies include emergent importation of vaccines and RIG, increasing designated hospitals for rabies vaccines storage, enhancing the HCPs training about PrEP and PEP. PEP is funded by government since 2013 July 24 if exposed persons are eligible by the guidance, and is scheduled to be covered under National Health Insurance in 2014.

(1). Importation:

The future requirement for rabies vaccine and RIG is under assessment according to the medically-attended animal bite surveillance data from “Real-time Outbreak and Disease Surveillance system”. For rapid expansion of the rabies vaccine stockpiles to fulfill the demands of persons who are indicated for PEP or PrEP, Taiwan CDC has maintained a close liaison with manufacturers to seek the supply of rabies vaccines and RIG since July 10th. Special importation projects have been implemented and the vaccines had been issued to the designated medical facilities since July 26th. Till September 24th, about 42,500 doses of vaccines have been purchased from Norvatis Taiwan and Sanofi Pasteur Taiwan to ensure the availability of vaccines for PEP and PrEP.

To be prepared and response to the re-emergence of rabies, pERIG has been purchased and delivered to regional centers of Taiwan CDC since August 4th. Till September 24th, there are 1,946 doses of HRIG (2 ml/vial), 250 doses of HRIG (10 ml/vial), and 2,000 doses of pERIG available.

(2). Regulation:

For precise and effective prescription of vaccines and RIG, the PEP administration was once regulated by application and verification individually according to the ACIP recommendations. Besides, persons in high risk groups are offered with PrEP according to lists from the Council of Agriculture and local county governments. For long term disease control and preparation, the regulatory policy has been changed to *ad hoc* audit, which means that the application would be reviewed randomly by authorized officials, since September 9.

(3). Distribution:

Before the rabies resurfacing in Taiwan, the rabies vaccines had been stored in twelve Taiwan CDC-contracted hospitals with travel medicine services. Since the first three rabid positive ferret-badgers were identified on July 18th, another three medical facilities in Nantou and Yunlin County have become the vaccine stockholders. The numbers of medical facilities with rabies immunizations increased to 28 on July 26th, 54 on August 5th, and 60 on August 9th. There is a vaccine-stored hospital in each of island counties, including Penghu, Kinmen, and Lianjiang, and 2-3 stockholders on average in other counties. Current accessibility of PEP and PrEP has increased remarkably [20].

(4). Training:

Taiwan CDC has published the “Guidance of human exposure to suspected rabid animals” [17], and cooperated with several medical associations to conduct series of education courses and seminars to strengthen the capacity of HCPs to manage persons exposed to suspected rabid animals.

Conclusion

Despite the high fatality of rabies, the disease can be prevented with adequate post-exposure prophylaxis. The burden of rabies can be reduced if the general populations and HCPs are capable of recognizing the exposure risks and are familiar with prophylactic measures.

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