

RABIES AND MANAGEMENT OF ANIMAL BITES

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ABSTRACT

Rabies is nearly 100% fatal and 100% preventable zoonotic disease. Rabies causes 50,000 deaths worldwide of which, more than 80% occur in India. Bite from any warm-blooded animal can transmit rabies. Management of animal bites from the point of view of prevention of rabies is a three-pronged policy: (a) Wound treatment, (b) antirabies serum and (c) antirabies vaccine (ARV). ARV can be given by both intradermal and intramuscular routes, however regimens, of both, are different. The minimum duration of re-exposure immunization is considered to be 3 months in a previously fully treated case of animal bite. There is also provision of preexposure prophylaxis in high-risk groups and children by both intramuscular and intradermal route.

Key words: Animal bites, management, rabies

INTRODUCTION

Rabies is a viral disease that affects the central nervous system and which is almost 100% fatal (whether treated or untreated) and India reports 80% of 50000 reported cases of rabies worldwide which is again presumed to be highly under-reported.

ETIOLOGY

Rabies is a highly neurotropic virus that defies immune surveillance by getting sequestered in the nervous system. Hence, there is no viremia, and the antibody response is delayed. It is a bullet shaped single-stranded RNA virus enveloped in a lipid membrane.

There is no age or sex predilection, but it is reported more from men of productive age group and children. 95% of cases in India are caused by dog bites.

Reservoir of infection

In India, the disease is reported

- Mainly from dogs and cats
- Sometimes from horses, sheep, goats, cows and buffaloes, foxes, donkeys, and pigs
- Occasionally, from elephants, camels, mongoose, jackals, and bears
- Not reported from bats and birds, however bats are important reservoir of infection and if a dead bat is found in a room where there were children, then it should be sent for examination from point of antirabies prophylaxis.

Rodents do transmit rabies; most common are mongoose and sewer rats. Other small rodents (squirrels, mice, rats usually die before being able to transmit disease and human disease has not been reported from these animals however possibility of transmitting rabies by these animals cannot be ruled out and individual discretion is recommended.

Modes of transmission

Rabies commonly spreads by:

- Bites, Scratches
- Contact on intact mucosa
- Licks on broken skin.

Rare modes of transmission are:

- Inhalation of aerosols containing virus
- Organ transplant from a person died of rabies (undiagnosed at the time of death).

Pathophysiology

After inoculation at the site of the bite, it enters the peripheral nerves. After prolonged and variable incubation period nucleocapsids spill into the myoneural junctions and enter the motor and sensory axons. Now the prophylactic therapy becomes ineffective. Rabies virus travels along axons at a rate of 12–24 mm/day to enter the spinal ganglion; here, its multiplication is heralded by the onset of pain or paresthesia at the site of the bite, which is the first clinical symptom and a hallmark finding. Here onwards virus spreads quickly at a rate of 200–400 mm/day into central nervous system (CNS), and the spread is marked by rapidly progressive encephalitis. From CNS, the virus spreads to periphery and salivary glands.

For the diagnosis and therapeutic opportunities, it is important to understand that rabies virus is not cytotoxic. Neuronal morphology and life span are normal throughout the

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disease course. The virion acts in the synaptic cleft where homology in amino acid sequences between receptors for acetylcholine, gamma-aminobutyric acid and glycine may afford a mechanism for viral binding. Thus, virion is neurotoxic rather than cytotoxic. Further, virus may not be replicating in the tissues although Negri bodies may be present.

Rabies is particularly of concern in children because:

- Because of short stature children are more susceptible to bites over face or upper part of the body
- Children cannot ward off animals easily
- Children are more likely to provoke animals
- Children may not report a bite due to fear of injections.

Clinical signs and symptoms

After a variable and sometimes prolonged incubation period the rabies is heralded by pain and/or paresthesia at the site of bite, then a prodrome of fever, lassitude etc., follows (like in any other viral illness). After a period of 4–7 day, the classical signs and symptoms of hydrophobia, aerophobia, and delirium follow. Death usually follows in 4–7 days depending on the climate, shorter in summers and longer in winter.

Classification of types of bites

The animal bites have been classified as follows:

World Health Organization recommendation on rabies postexposure treatment^[1]

There are three World Health Organization Categories depending on the type of contact with the suspect animal.

Category I

Type of contact with the suspect animal: Touching or feeding of animal and/or licks on intact skin.

Recommended treatment: None if reliable case history is available.

Category II

Type of contact with the suspect animal: Nibbling of uncovered skin, Minor scratches or abrasions without bleeding, licks on broken skin.

Recommended treatment - Administer vaccine immediately, stop treatment, if animals remain healthy throughout an observation period of 10 days or if the animal is euthanized and found to be rabies negative by appropriate laboratory techniques.

Category III

Type of contact with the suspect animal: Single or multiple intradermal bites or scratches. Contamination on the mucous membrane with saliva (i.e. licks).

Recommended treatment - Administer rabies vaccine and immunoglobulin immediately. Stop the treatment, if animals

remain healthy throughout an observation period of 10 days or if the animal is euthanized and found to be rabies negative by appropriate laboratory techniques.

World Health Organization classification is rather confusing. This is to be made very clear and the point to remember is that size, site, and number of bites do not matter as long as they are transdermal. Either there is a bite, or there is not.

Patients reporting to doctors usually have bites. If there is a bite, it is to be treated as category III bite. In category II as well, when a patient is coming to the doctor, should be given benefit of the doubt and should be treated as class III. Rabies is a gruesome and 100% fatal disease and doctor should not leave any chance.

Treatment of rabies

Rabies is almost 100% fatal disease. However, as already cited above it is neurotoxic and not cytotoxic. The neuronal structure remains normal in the disease course. So, if the acute episode is taken care of by inducing coma, the natural defense mechanism can take over and patient can survive. There are some reports of rabies patients surviving after induced coma treatment. However, none of them had hydrophobia and diagnosis of rabies was made by antibody measurement, and no viral antigen was detected.

Prophylaxis of rabies

The diseases that cannot be treated must be prevented. Same is true for rabies also.

The principal of prophylaxis are as follows:

- 1/3 Wound treatment
- 1/3 antirabies serum (ARS)
- 1/3 antirabies vaccine (ARV).

Wound treatment

Wound should be washed with soap and running water for at least 10 min. If there is no running water, it can be poured from a jug. Povidone iodine should be applied. As far as possible wound should not be stitched as it increases the trauma to nerve endings. If mandatory, loose sutures may be applied to control bleeding that too under ARS cover. Never apply irritants or cauterize the wound. Thorough wound toilet decreases the viral load by 95%. The soap or detergent dissolves the lipoprotein membrane and thus renders the virus ineffective.

Anti-rabies serum

Anti-rabies immunoglobulins are preformed antibodies that coat the virus and prevent its entry into a nervous system resulting in obliteration of viral load. There are two generic types of ARS:

- Human rabies immunoglobulin (HRIG)
- Equine rabies immunoglobulin (ERIG).

Human rabies immunoglobulin is produced from the plasma of human donors, and ERIG is produced from the horses.

Human rabies immunoglobulin has less foreign protein so is associated with lesser side effects but it is expensive and there can be transmission of hepatitis B, C, or HIV in case of a mishap. ERIG, on the other hand, is cheaper but contains foreign protein, and there can be hypersensitivity. The doses of HRIG and ERIG are as follows:

Human rabies immunoglobulin - 20 units/kg body weight, There is an upper limit of 1500 units of maximum dose.

Equine rabies immunoglobulin - 40 units/Kg body weight, There is an upper limit of 3000 units of maximum dose.

Rabies immunoglobulin is indicated in all transdermal bites irrespective of the size and number of bites. So, if the bite is a pinpoint one or a massive one the RIG has to be given. In other words, patients presenting to clinician with any bite with bleed is a candidate for RIG. This covers an almost entire population of animal bite patients presenting for treatment. Almost all the cases of vaccine failure in case of rabies are because of not giving the RIG. The immunoglobulins are also indicated in all mucosal exposure as they are category III exposure. Intact mucosa is not a barrier to rabies virus.

Rabies immunoglobulin should be infiltrated around wound as much as possible and if anything remains it should be given at the deltoid/antero-lateral thigh (in smaller children). In no case, the dose of ARS should be more than the prescribed dose as per body weight because excessive ARS will neutralize the vaccine which is also to be given along with it. If the wound is large and the volume of ARS is not enough to infiltrate the wound, then ARS should be diluted in normal saline and infiltrated around the wound. ARS should never be given intravenously. ARS can be given up to 7th day of ARV schedule if not given on day 0. After day 7 giving ARS, may interfere with the antibody response. ARS and ARV should not be mixed in the same syringe or should not be given at same anatomic site. RIGs provide immediate protection which lasts up to 21 days, so they have to be backed by ARVs. All immunoglobulin should be given after sensitivity test only. Due precautions should be observed for other vaccine like measles, mumps, rubella, etc., as immunoglobulins may interfere with the immune response of these vaccines as well.

Anti-rabies vaccines

In 1885, Pasteur developed first ARV from desiccated spinal cord of a rabbit who died of rabies. Semple produced sheep/goat brain vaccine in 1911, which was prevalent up to 2006 when it was discontinued because of availability

of much safer and more effective tissue culture vaccines. We have human diploid cell culture vaccine, chick embryo vaccine, vero cell vaccine, duck embryo vaccines. All the vaccines are effective. The dose schedule for intramuscular injections is as follows (also called Essen schedule).

(Human diploid cell vaccine [HDCV]/purified chick embryo vaccine [PCEV]): 1.0 ml intramuscular on 0, 3, 7, 14, 28/30 days.

Purified vero cell vaccine: 0.5 ml intramuscular on 0, 3, 7, 14, 28/30 days.

Where day 0 is the day of the start of vaccination schedule.

Along with the wound care and RIG, the ARV is to be given to all transdermal bites and mucosal exposure patients. ARV must be given in the deltoid/antero-lateral thigh area only and any vaccine given in the gluteal region must be considered null and void.

Intradermal schedule

Drug controller of India has also ratified the modified Thai red cross schedule which is as follows [Table 1]:

0.1 ml × 2 (at two sites) on 0, 3, 7 and 28 day.

It reduces the total amount to be given to 0.8 ml/person as against 5 ml/person in Essen regimen, and it also abolished one visit on 14th day. However, the vial is supplied in 1 ml reconstituent in both PCEV and purified vero rabies vaccine (PVRV). The reconstituted vaccine should be kept at 2–8° temperature and must be used within 4 h. It requires trained staff and proper cold storage facilities in the vaccination room. However, it reduces the cost dramatically which is very important in the resource-poor settings.

Vaccine schedule is same for all age groups.

Re-exposure

In patients who were fully vaccinated by ARS and ARV, if bitten by rabid animal again, are to be given two doses on day 0 and 3. The dose in case of intramuscular regime is 1.0/0.5 ml as per vaccine and 0.1 ml in case of intradermal regime. The doses are only two irrespective of the time interval after the last bite management.

Preexposure prophylaxis

Newer tissue culture vaccines are safe and effective; they can be given even before the bite takes place. This is of importance in pediatric age group because children may not

Table 1: Drug controller general of India recommended post-exposure IM and ID regimens: Summary^[2]

Regimen	Day 0	Day 3	Day 7	Day 14	Day 21	Day 28	Day 90	Vials	Visits
Essen (ml)	1.0	1.0	1.0	1.0	-	1.0	-	5	5
Regimen	Day 0	Day 3	Day 7	Day 14	Day 21	Day 28	Day 90	ml	Visits
Thai red cross (updated) (ml)	2x0.1	2x0.1	2x0.1	-	-	2x0.1	-	<1	4

tell about animal bite because of fear of injections. There are two regimens as follows:

- Intramuscular schedule: 1.0/0.5 ml on 0, 7, 21/28 days or 0, 28, 56 days
- Intradermal schedule: 0.1 ml HDCV/PVRV or 0.2 ml of PCEV/PCEV on 0, 7, 21/28 days.

All the vaccines are safe and effective for both pre and postexposure prophylaxis and i/m or i/d schedules. However, as far as possible they should not be interchanged.

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