

Death from rabies: The reason being poor compliance to vaccination or it's failure

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ABSTRACT

Rabies is endemic in India and responsible for 20,000 human deaths every year. It is 100% preventable when the vaccine is taken along with proper wound care and rabies immunoglobulin administration though update continues regarding the requirement of the number of vaccine doses, the need for immunoglobulin, and if required their types. We study four cases of rabies having street dogs' bite category grade 3. Everyone took vaccines at least three doses but none of them took rabies immunoglobulin. They developed symptoms of rabies with a gap of 15–28 days after the bites and admitted to a tertiary care center. One patient was left against medical advice and three patients were treated according to the modified Milwaukee protocol. But, none of them could be saved. So, it may be proposed that the reason of deaths may be due to lack of administration of rabies immunoglobulin (passive vaccination) or failure of vaccines. Hence, the government may focus on the administration of complete and quality post-exposure prophylaxis in all cases of animal bites. Although Milwaukee protocol saves few lives, it may be further improved or other treatment modalities may be developed for rabies treatment.

Keywords: Dog bite, Milwaukee protocol, post-exposure prophylaxis, rabies immunoglobulin

Introduction

Rabies is endemic in India responsible for 20,000 human deaths every year.^[1] The dog is responsible for 99% of human cases in endemic regions.^[2] There is no effective treatment to date. A treatment modality named the Milwaukee Protocol is hope but could not succeed much.^[3] Vaccine is available which is 100% effective if taken properly. Some studies have reported deaths due to deviation from WHO guidelines of post-exposure prophylaxis (PEP) which is expected. And some studies have reported true failure that is, patients develop rabies despite appropriate PEP.^[4] But this is not expected. Hence it is difficult

to say whether incomplete vaccination or vaccine failure is the cause of rabies in recent times.

Thereby, we report a case series of four recent rabies deaths despite the initiation of at least three doses of vaccines (active immunity) reflecting possible vaccine failure or rarely due to lack of RIG administration.

Case Presentation

We received four cases of rabies last year. The demography, clinical details, laboratory findings, treatment, and outcomes were described in Table 1.

All of them had a history of dog bites in the last 15–28 days. Two patients were bitten in the upper part of the body (face and hand), while the other two were bitten in lower limbs. All had received 3–5 doses of vaccines, none received rabies immunoglobulins. Out of four patients, one patient had a paralytic form of rabies

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Table 1: The demography, clinical, laboratory, treatment, and outcome details of four rabies patients

Case no.	Age/sex	Nature of animal	Post-exposure prophylaxis (PEP)	Chronology of events (Clinical features)	CSF findings	Diagnosis considered	Confirmatory tests	MRI findings	Treatment	Outcome
1.	29/M	Street dog - killed soon	Five doses, Purified chick embryo cell vaccine, Rabipur (0, 3, 7, 14, 21), no rabies immunoglobulin	Dog bite, category-3, @right chin – 28 days Fever and flaccid quadriplegia-5 days cough-2 days	Total cells -850 Monomorphs - 88% Polymorphs -12% Protein-88 Sugar-68 (corresponding sugar-128) Negative staining	Rabies (paralytic form)	Rising serum and CSF virus-neutralizing antibody titer of 1:2048 and 1:32768 respectively after 10-days of the previous sample any restricted diffusion or contrast enhancement on day-2	Mild hyperintensities in B/L basal ganglia, thalamus, medial temporal lobe, midbrain, respectively after and dorsal pons without any restricted diffusion or contrast enhancement on day-2	Modified Milwaukee protocol from day-1	Expired on 28 days of admission
2.	58/F	Street dog - killed soon	Three doses, Purified chick embryo cell vaccine, Rabipur (0, 3, 7), no rabies immunoglobulin	Dog bite, category-3, at the right side of nose -20 days Paresthesia of face-20 days Fever and restlessness-5 days Altered sensorium -1 day	Total cells-5, Monomorphs - 100% Protein-126, Sugar-71 (corresponding sugar-153) Negative staining	Rabies encephalitis	Rising serum and CSF virus-neutralizing antibody titer of 1:8192 and 1:2048 respectively after 5-days of the previous sample	Bilateral brainstem mild hyperintensities without any restricted diffusion or contrast enhancement on day-2	Modified Milwaukee Protocol from day-1	Hospital survival of 16 days but died after one day due to LAMA
3.	38/M	Street dog - status unknown	Three doses, vaccine type unknown (0, 3, 7), no rabies immunoglobulin	Dog bite, category-3, at left mid-calf -15 days Dysphagia and restlessness-3 days	Not done due to LAMA	Rabies encephalitis	Not done due to LAMA	Not done due to LAMA	Supportive since protocol could not be started after 2 days	LAMA on the same day of admission and 2 of admission
4.	34/M	Street dog - status unknown	Three doses, vaccine type unknown (0, 3, 7), no rabies immunoglobulin	Dog bite, category-3, at right dorsum foot -17 days Dysphagia and restlessness-3 days Dyspnoea and hydrophobia-2 days	Total cells-60, Monomorphs - 100% Protein-84, Sugar-58 (corresponding sugar-122) Negative staining	Rabies encephalitis	Rabies RNA PCR positive from CSF and serum but virus-neutralizing antibody titer negative	Not done due to early death	Modified Milwaukee protocol from day-1	Expired on day 2 of admission

Modified Milwaukee protocol: Infusions - ketamine, midazolam, and human insulin; Injections - methylprednisolone; Tablet - amantadine, fludocortisone, and Vit-C, LAMA – Left against medical advice

and the other three had encephalitis form, suggested with MRI brain and spine and confirmed with paired rising CSF antibody titers or positive RNA [Table 1].

All patients were managed in an isolation ward with ventilator support, barrier nursing, and strict standard precautions. Modified Milwaukee protocol (since haloperidol, various laboratory monitoring, and regular virological monitoring were not followed and methylprednisolone pulse therapy was administered as per our neurologist consultation contrast to original protocol) was followed in three cases. All were died in due course of time either at the hospital or home after telephonic confirmation [Table 1].

Discussion

We report four vaccinated rabies deaths who did not receive rabies immunoglobulins (RIG). These cases may entail incompleteness or failure of vaccination.

Proper wound washing with soap and water can prevent rabies cases in one-third of cases.^[5] Poor and illiterate persons are not aware of this step. Probably, none of our cases would wash their wound properly which would contribute to death.

RIG administration is a very crucial step for preventing rabies. Rabies vaccines induce antibody response only after 7–14 days of a PEP regimen.^[2] Immediate administration of RIG at the bite site slows down or stops viral progression and increases patient survival.^[6] Gaddekar *et al.* reported two patients bitten by same rabid dog.^[7] Both patients had a Grade 3 bite. One patient properly followed the vaccination guidelines and got completely cured. Another patient took a vaccine but without wound cleaning and RIG and developed rabies. Some other studies also point towards improper or non-administration of RIG.^[8,9] So, lack of immunoglobulin administration was probably the reason for vaccine failure in all of our cases. However, the WHO 2018 vaccine position paper stated that wound washing and complete PEP vaccine can prevent rabies in more than 99% cases even in absence of RIG.^[2] Chandalu J *et al.* also mentioned 473 cases who escaped rabies after receiving PEP (at least 3 vaccines completed) without RIG.^[10] If this is true, then our cases died not because of a lack of RIG administration but may be of other cause.

However, true failures without recognized defects in PEP management have also been reported. A case report was published in the newspaper “Hindustan Times” (17 April 2015) that revealed a girl with grade 3 bite received appropriate wound care, RIG, and Rabipur vaccine within 10–12 hours of the bite.^[11] But, she developed rabies and died. Wilde *et al.* reported 15 rabies cases.^[12] Seven cases developed rabies due to errors in management. But, eight cases developed rabies despite receiving appropriate PEP, though, these had bite sites on highly innervated zone like face or hands or multiple bite sites. Hence these suggest the possibility of true failure of vaccines. The same thing could have happened in our four cases.

Adherence to PEP vaccination and immunoglobulin in India is very low, 20.9%, and 1.3% respectively as described by Sudarshan *et al.*^[13] Higher cost and non-availability of RIG at health care centers are two limiting factors. The cost of equine RIG (eRIG) and human RIG (hRIG) in India, for an average patient of 60 kg bodyweight, are approximately US \$20 and the US \$500 respectively which are very costly for the general population of India. Bharti *et al.* proposed an alternative method—all the bite sites infiltration with RIG, but not according to body weight. So, the remaining amount may be available for other patients.^[14] It is more economic as well as to make availability of RIG even in short supply. Based on a study in BHK 21 cells & Swiss albino mice, Madhusudana *et al.* found that the dose of RIG can be minimized by at least 16 times than the presently used dose.^[15] But, it needs further optimization in human beings. Mass dog vaccination is another approach that can be helpful for the containment of rabies. If 70% of dog vaccination would be implemented under the annual pulse vaccination program over several years, rabies could be eliminated from dogs. This step is taken in different countries of Africa, Asia, Europe, and America.^[16] Government of India may provide RIG free of cost to general people similar to the government of Tunisia or open “Bite treatment center” in endemic zones as in Philippines.^[17,18]

There is a tenet “If a patient has rabies, he will die in the next few days; if he does not die, he does not have rabies!” There are only 29 reported cases of rabies survivors worldwide to date.^[19,20] In our study, cases 1, 2, and 4 were managed according to the modified Milwaukee protocol. Case 1 and 4 failed but case 2 was showing some signs of improvement (volume control ventilation reduced to pressure support ventilation and GCS-E1VtM1 to GCS-E3VtM1) but got LAMA before we could derive any conclusion. High-quality intensive care support may give more motivation to researchers to unravel the mechanisms to defeat the rabies infection.

Conclusions

- All patients must receive RIG in category 3 animal bites. Dose optimization may be done to be more economic.
- The government may try to provide free RIG for all or establish a “Bite treatment center” in highly endemic zones.
- Vaccine failure may be one of the concerns for rabies deaths where patients received at least 3 doses. So, there should be updated quality validation in available vaccinations. We should also think of a new strain of the virus.
- Newer treatment strategies and effective anti-rabies medications need to be explored.

Ethical clearance

We have obtained ethical clearance and waiving of consent from the institute.

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Conflicts of interest

There are no conflicts of interest.

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