Survival in human rabies but left against medical advice and death followed – Community education is the need of the hour

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Abstract
Human survival after developing rabies is very scary to humanity. We report a case of a 58-year-old woman from Uttar Pradesh (north India), who presented with 5-days of fever and 1-day of altered sensorium associated with agitation, hydrophobia, and bedwetting after 20 days of WHO category 3 bite in the face by a rabid dog. She had taken three doses of anti-rabies vaccinations but not immunoglobulin of postexposure prophylaxis. Laboratory investigation showed a rising titer of virus-neutralizing antibodies in both serum and cerebrospinal fluid (CSF). We treated the patient according to the modified Milwaukee protocol. The patient remained to survive and had a recovery trend during hospital stays of 15 days before relatives took her left against medical advice (LAMA). As we know rabies has approximately 100% mortality rate but by using the aggressive treatment approach (like Milwaukee protocol), the patient may survive. Rabies can be effectively prevented by using adequate postexposure vaccine prophylaxis and rabies immunoglobulin (in category-3) after bite of a rabid animal. Our report along with other published reports should give more motivation to clinicians and education to the public to have an intensive treatment approach and patience, respectively to make rabies survival.

Keywords: Dog bite, Milwaukee protocol, postexposure prophylaxis, rabies encephalitis, rabies immunoglobulins

Background
Rabies, a zoonotic disease after biting of rabid animals, is the most feared human infections with the highest case fatality rate, approximately 100%. Rabies virus being neurotropic travels retrogradely to diencephalon, hippocampus, and brainstem and causes neuronal dysfunction such as autonomic instability leading to death. Mitochondrial dysfunction of neurons due to oxidative stress leads to such types of abnormalities. The incubation period varies from days to years depending upon various factors such as the location of the entry wound, the severity of the wound, the animal’s immune system, and viral load. Clinical rabies manifests mainly in two forms, encephalitic (furious – more common) and paralytic (dumb) rabies. However, death is a signature in both types due to a lack of anti-rabies drugs.

There are only 29 reported cases of rabies survivors worldwide to date; the last case was reported in India in 2017. Out of which 3 patients (10.35%) were survived by using the Milwaukee protocol and other patients survived with intensive care support. The major reason for survival was the highest level of critical care support. This has to reach to the community since it is taken in granting that rabies means death. Hence rarely treatment is tried to make survive.

We report another patient with this deadly disease who survived during hospital stays with the help of modified Milwaukee protocol and intensive critical care support.

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Table 1: A Literature review of cases of human rabies with survival

| Location      | Year | Age/sex (ref) | Transmission | Immunization prior to onset | Clinical Management | Outcome            |
|---------------|------|---------------|--------------|----------------------------|---------------------|--------------------|
| United States | 1970 | 6/M<sup>1<sup>4</sup> | Dog bite     | Duck embryo vaccine         | Supportive           | Complete recovery |
| Argentina     | 1972 | 45/F<sup>1<sup>4</sup> | Dog bite     | Suckling mouse brain vaccine| Supportive           | Moderate sequelae |
| United States | 1977 | 32/M<sup>1<sup>4</sup> | Laboratory   | Pre exposure vaccination    | Supportive           | Severe sequelae   |
| Mexico        | 1992 | 9/M<sup>4</sup>    | Dog bite     | Post exposure vaccination   | Supportive           | Severe sequelae   |
| India         | 2000 | 6/F<sup>4</sup>    | Dog bite     | Postexposure therapy        | Supportive           | Severe sequelae   |
| United States | 2004 | 15/F<sup>4</sup>   | Dog bite     | No postexposure vaccination | Milwaukee protocol   | Mild sequelae     |
| Brazil        | 2008 | 15/M<sup>4</sup>   | Dog bite     | Postexposure vaccination    | Milwaukee protocol   | Severe sequelae   |
| Turkey        | 2008 | 17/M<sup>4</sup>   | Dog bite     | Postexposure vaccination (one dose) | Supportive | Complete recovery |
| USA (Texas)   | 2009 | 17/F<sup>4</sup>   | Dog bite     | No postexposure vaccination | Supportive           | Complete recovery |
| India         | 2010 | 8/M<sup>4</sup>    | Dog bite     | Postexposure vaccination and rabies immunoglobulin | Supportive           | Severe sequelae   |
| India         | 2011 | 17/M<sup>4</sup>   | Dog bite     | Post exposure vaccination   | Supportive           | Severe sequelae   |
| India         | 2011 | 13/F<sup>4</sup>   | Dog bite     | No post exposure vaccination or RIG | Supportive | Complete recovery |
| USA (California) | 2011 | 8/F<sup>4</sup>    | Possible Cat bite | No post exposure vaccination | Modified Milwaukee protocol | Mild sequelae |
| South Africa  | 2012 | 4/M<sup>4</sup>    | Dog bite     | Post exposure vaccination (one dose) | Supportive | Moderate sequelae |
| Chile         | 2013 | 25/M<sup>4</sup>   | Dog bite     | Post exposure vaccination   | Supportive           | Severe sequelae   |
| India         | 2014 | 16/M<sup>4</sup>   | Dog bite     | Post exposure vaccination   | Supportive           | Severe sequelae   |
| India         | 2014 | 6/M<sup>4</sup>    | Dog bite     | Post exposure vaccination and rabies immunoglobulin | Supportive, steroid, IV immunoglobulins | Severe sequelae |
| India         | 2014 | 13/M<sup>4</sup>   | Dog bite     | Post exposure vaccination   | Supportive, broad spectrum antibiotic, antiepileptics | Severe sequelae |
| India         | 2015 | 10/M<sup>4</sup>   | Dog bite     | Post exposure vaccination   | Supportive           | Unknown           |
| India         | 2015 | 5/M<sup>4</sup>    | Dog bite     | Post exposure vaccination   | Supportive           | Unknown           |
| India         | 2015 | 18/F<sup>4</sup>   | Dog bite     | Post exposure vaccination and equine rabies immunoglobulin | Supportive           | Mild sequelae     |
| India         | 2015 | 10/M<sup>4</sup>   | Dog bite     | Post exposure vaccination   | Supportive           | Severe sequelae   |
| Ghana         | 2016 | 36/M<sup>4</sup>   | Dog bite     | No postexposure therapy     | Supportive, antibiotic complete recovery | Severe sequelae |
| India         | 2016 | 5/F<sup>4</sup>    | Dog bite     | Post exposure vaccination   | Supportive           | Severe sequelae   |
| India         | 2017 | 26/M<sup>4</sup>   | Dog bite     | Post exposure vaccination   | Supportive           | Moderate sequelae |
| India         | 2017 | 9/M<sup>4</sup>    | Dog bite     | Post exposure vaccination and equine rabies immunoglobulin | Supportive           | Mild sequelae     |
| India         | 2017 | 4/M<sup>4</sup>    | Dog bite     | Post exposure vaccination and equine rabies immunoglobulin | Supportive           | Severe sequelae   |
| India         | 2017 | 3/F<sup>4</sup>    | Dog bite     | Post exposure vaccination   | Supportive           | Moderate sequelae |
| India         | 2017 | 5/F<sup>4</sup>    | Dog bite     | Post exposure vaccination and human rabies immunoglobulin | Supportive           | Severe sequelae   |
| India         | 2019 | 58/F<sup>4</sup>   | Dog bite     | Postexposure prophylaxis (three doses of vaccine without immunoglobulin) | Modified Milwaukee protocol | Hospital survival but death due to LAMA |

**Case Report**

A 58-year-old woman from Bijnor, Uttar Pradesh (North-India) with no significant past illness, medication history, or travel history presented with 5-days duration of acute onset fever that was high grade, continuous, associated with headache, and nonbilious vomiting. She had altered sensorium since day 1 of progressive nature and fluctuating course associated with agitation, incomprehensible speech, hydrophobia, and bedwetting. Relatives gave a history of category-3 dog (street) bite over the left facial area near nose 20 days back and took three doses of postexposure prophylaxis of purified chick embryo cell rabies vaccine on the next day (18 h) of bite. However, she had not received any anti-rabies immunoglobulin. She had local paresthesia symptoms over the left face since then. The dog was killed by villagers to protect themselves from being bitten by a dog but not being examined in the laboratory.

On examination, the patient was semi-comatose (GCS, E4V2M2). She had drooling of saliva and vitals of BP = 110/70 mmHg (fluctuating up to 160/90 mmHg), PR = 120/min (fluctuating up to 157/min), RR = 22/min, and temp = 98.8°F. On detailed CNS examination, she had normal size right pupil with reaction to light and left side ptosis bulbi (from birth). She had no neck rigidity/stiffness. The tone was within normal limits, power could not be assessed, deep tendon reflexes exaggerated, and plantar B/L flexor. Rest examinations were unremarkable.

Considering her demography and clinical presentation, few differentials were considered. These were rabies encephalitis, herpes meningoencephalitis, tubercular meningoencephalitis,
Rabies is a fatal disease accounting at least 60,000 deaths per year. A palliative or aggressive approach is required for suspected or confirmed rabies patients. However, maximum cases are deprived of treatment with the hospital mindset that the disease is having a 100% death rate, then why to waste resources. With the passage of time, few physicians have tried interventions to make them survive. As a result, there have been few well-documented rabies survivors until now [Table 1]. Before 2004, only five cases were survived who received incomplete PEP. Ideally, PEP should begin immediately after animal bite as soon as the washing of all wounds with soap and water, so that viral load can be reduced at the site of inoculation. The most common causes of failure of PEP are (1) lack of use of rabies immunoglobulin, (2) not all wounds are injected with immunoglobulin, (3) a 6-day delay in the prophylaxis, (4) suturing of wounds before immunoglobulin injection, and (5) wounds in the highly innervated region of the body such as face and hand. In our cases, the reason for PEP failure was due to all these reasons.

However, after 2004, more cases are being documented to have survival. In 2004, a teenager survived who had not rabies vaccinations (pre-exposure or postexposure; active or passive) and been treated using an experimental Milwaukee protocol having induced coma and antiviral treatment. This protocol is...
mainly aimed to suppress the brain activity that would minimize the damage while the patients’ immune system develops at an adequate immune response.[17] As reviewed, it was applied on 36 rabies patients out of which 5 cases (13.8% success rate) survived (two with Milwaukee protocol version 1 and three from version 2 where the use of rabiesin was omitted).[18] Though it is noted that low success rate and high costs of the protocol are strong factors towards nonacceptance as an effective treatment; this protocol has imbibed many research scientists to think and apply on various aspects of aggressive treatment options. If you see all the survived cases (24 including our case) after 2004, all have used aggressive critical care options. Hence, the intensive approach may be modified Milwaukee protocol is the solution to survive rabies.

Among the thirty documented survivors (including ours), four cases were bitten by bats [Table 1]. Bat associated rabies virus is thought to be less virulent and associated with a good prognosis. Five survivors did not receive any PEP, six received vaccines as well as immunoglobulins, and all other patients received only vaccines. Hence, other factors like an aggressive treatment approach are to be considered for making survival when the patient is not immunized or even partial immunized. This has to be incorporated into the mind of primary care physicians who frequently deal with rabies patients.

There are good and bad prognostic factors in rabies as reviewed in Table 2.[19] Our case had four good prognostic factors (previously healthy, early clinical rabies, negative antigen and positive antibody test, and critical care facilities) compared to three bad ones (older age, no previous rabies vaccination, and dog bite). Our case was weaning from ventilation and eye-opening was achieved but she had not shown any limb movements that may show she was in a vegetative state similar to many survived previous cases with the severe sequel. This may be explained due to old age and dog rabies.

In conclusion, even after three doses of timely active vaccination in cases of a dog bite, rabies can occur. Rabies can be effectively prevented by adequate postexposure prophylaxis after bite of a rabid animal and not miss immunoglobulin administration to old age and dog rabies.

| Good prognosis                                                                 | Bad prognosis                                                                 |
|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Younger age                                                                   | Older age                                                                     |
| Previously healthy                                                            | Medical comorbidities                                                         |
| History of previous rabies vaccination                                         | No previous rabies vaccination                                                |
| Early clinical rabies                                                          | Late clinical rabies                                                          |
| Infection by the bat rabies virus                                              | Infection by the dog rabies virus                                             |
| A negative test for rabies virus antigen/RNA and positive for antirabies antibody | A positive test of rabies virus antigen/RNA and negative for neutralizing anti-rabies antibodies |
| Access to critical care facilities                                             | Lack of access to critical care facilities                                    |

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In conclusion, even after three doses of timely active vaccination in cases of a dog bite, rabies can occur. Rabies can be effectively prevented by adequate postexposure prophylaxis after bite of a rabid animal and not miss immunoglobulin administration in blood oozing bites by community physicians. By using the aggressive treatment approach (modified Milwaukee protocol), the patient may survive from rabies. Our report along with other published reports should give more motivation to clinicians to have an intensive treatment approach and higher education to the public to have the patience to make rabies patient survival.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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