Case Report

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.[1] 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.[2,3] 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 [Table 1]. 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[4]	Bat bite	Duck embryo vaccine	Supportive	Complete recovery
Argentina	1972	45/F[4]	Dog bite	Suckling mouse brain vaccine	Supportive	Moderate sequelae
United States	1977	32/M[4]	Laboratory	Pre exposure vaccination	Supportive	Severe sequelae
Mexico	1992	9/M[4]	Dog bite	Post exposure vaccination	Supportive	Severe sequelae
India	2000	6/F[4]	Dog bite	Postexposure therapy	Supportive	Severe sequelae
United States	2004	15/F[4]	Bat bite	No postexposure vaccination	Milwaukee protocol	Mild sequelae
Brazil	2008	15/M[4]	Bat bite	Postexposure vaccination	Milwaukee protocol	Severe sequelae
Turkey	2008	17/M[5]	Dog bite	Postexposure vaccination (one dose)	Supportive	Complete recovery
USA (Texas)	2009	17/F[4]	Bat bite	No postexposure vaccination. Vaccination and RIG provided as part of management.	Supportive	Complete recovery
India	2010	8/M[6]	Dog bite	Postexposure vaccination and rabies immunoglobulin	Supportive	Severe sequelae
India	2011	17/M[4]	Dog bite	Post exposure vaccination	Supportive	Severe sequelae
India	2011	13/F[4]	Dog bite	No post exposure vaccination or RIG	Supportive	Complete recovery
USA (California)	2011	8/F[4]	Possible Cat bite	No post exposure vaccination. Vaccination and RIG provided as part of management.	Modified Milwaukee protocol	Mild sequelae
South Africa	2012	4/M[4]	Dog bite	Post exposure vaccination (one dose)	Supportive	Moderate sequelae
Chile	2013	25/M[7]	Dog bite	Post exposure vaccination	Supportive	Severe sequelae
India	2014	16/M[8]	Dog bite	Post exposure vaccination	Supportive	Severe sequelae
India	2014	6/M[9]	Dog bite	Post exposure vaccination and rabies immunoglobulin	Supportive, steroid, IV immunoglobulins	Severe sequelae
India	2014	13/M[10]	Dog bite	Post exposure vaccination	Supportive, broad spectrum antibiotic, antiepileptics	Severe sequelae
India	2015	10/M[11]	Dog bite	Post exposure vaccination	Supportive	Unknown
India	2015	5/M[12]	Dog bite	Post exposure vaccination	Supportive	Unknown
India	2015	18/F[11]	Dog bite	Post exposure vaccination and equine rabies immunoglobulin	Supportive	Mild sequelae
India	2015	10/M[12]	Dog bite	Post exposure vaccination	Supportive	Severe sequelae
Ghana	2016	36/M[13]	Dog bite	No postexposure therapy	Supportive, antibiotic	complete recovery
India	2016	5/F[12]	Dog bite	Post exposure vaccination	Supportive	Severe sequelae
India	2017	26/M[12]	Dog bite	Post exposure vaccination	Supportive	Moderate sequelae
India	2017	9/M[12]	Dog bite	Post exposure vaccination and equine rabies immunoglobulin	Supportive	Mild sequelae
India	2017	4/M[11]	Dog bite	Post exposure vaccination and equine rabies immunoglobulin	Supportive	Severe sequelae
India	2017	3/F[12]	Dog bite	Post exposure vaccination	Supportive	Moderate sequelae
India	2017	5/F[12]	Dog bite	Post exposure vaccination and human rabies immunoglobulin	Supportive	Severe sequelae
India	2019	58/F (this report)	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 phthisis 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,

scrub encephalitis, another infective encephalopathy, metabolic encephalopathy, and central nervous system vasculitis. However, rabies is considered the most.

The patient's hematological and biochemical parameters were within normal limits. Screening tests for common infections were negative. Cerebrospinal fluid (CSF) analysis revealed 5 cells with all monomorphs, protein-126 mg/dL, sugar-71 mg/dL (corresponding blood sugar-153 mg/dl), and negative staining (gram stain, acid-fast staining, India ink preparation).

The initial magnetic resonance imaging (MRI) of the brain showed bilateral brainstem hyperintensities, suggestive of rabies encephalitis [Figure 1a and b]. Paired serum and CSF samples for rabies antibody titers and RT-PCR for viral RNA were sent to a reference lab (NIMHANS, Bengaluru). The samples were negative for rabies RT-PCR but rabies virus neutralizing antibody titers by rapid fluorescence focus inhibition test in serum and CSF were 8192 IU/mL and 2048 IU/mL, respectively that demonstrated a significant rise in titer compared to previous sample (5 days apart), hence confirming rabies.

The patient was managed in the isolation ward with ventilator support, barrier nursing, and strict standard precautions with modified Milwaukee protocol.

During hospital day (HD), 0–7 days: the patient was intubated and kept under sedation with infusions of ketamine (0.5–1 mg/kg/h) and midazolam (2 mg/h) having a target to achieve deep sedation. Ventilator settings were VC mode, tidal volume 350 mL, PEEP 6 cm of H2O, respiratory rate 14/min, and Fio2 60%. Monitoring was going on every hourly; hypocarbia was avoided. CVP line, NG tube, and urinary catheter were placed. Euvolemia was maintained with fluids (NS/RL). Other therapies as per protocol were methylprednisolone (chosen over dexamethasone pulse after consultation with our neurologist to take care autoimmune demyelinating encephalomyelitis) pulse therapy 1 g/day for 5 days followed by oral dexamethasone 8 mg TDS with tapering over the next 7 days; low-dose insulin infusion (0.5 U/h along with continuous dextrose infusion with RBS monitoring having target of 140–180 mg/dL); amantadine of 250 mg BD; cap vitamin-C of 250 mg BD; fludrocortisone of 0.1 mg TDS; DVT prophylaxis; and twice daily electrolytes monitoring.

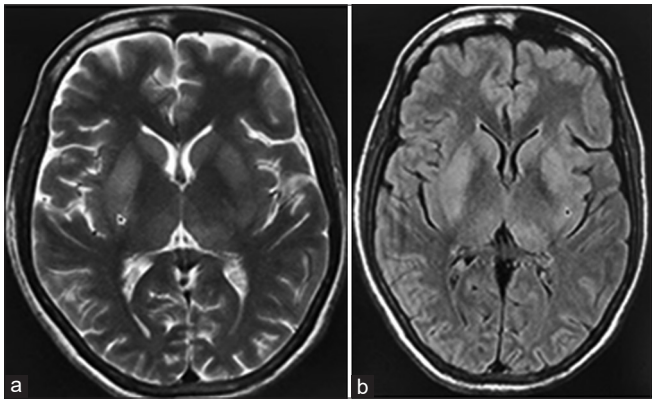

Figure 1: Magnetic resonance imaging of brain; (a) T2W image (b) FLAIR image showing mild hyperintensities in bilateral basal ganglia (arrows) without diffusion restriction or hemorrhages on the gradient (not shown)

On HD, 7–14 days, we continued supportive therapy, tapered sedation aggressively and stop by day 12. She opened her single functioning eye on day 10 and had eye contact (GCS – E3VtM1). However, we continued low-dose insulin, amantadine, vitamin-C, fludrocortisone, and tapered dexamethasone.

On day 12, tracheostomy was done and the mode of a ventilator was changed from VC to SIMV and then to PSV in 48 h. On day 15, the patient had GCS – E4VtM1, the patient was on improving trend but her attendant was not ready to stay further despite repeatedly counseling and went to leave against medical advice (LAMA) on Ambu bag with premature termination of treatment.

She was followed up telephonically, however, she had expired in 12 h after reaching home (next day of discharge).

Discussion

We report an old-aged woman who presented in the encephalitic state after 20 days of a street rabid dog bite of category-3. She took incomplete postexposure prophylaxis (PEP) without rabies immunoglobulins. She was treated on modified Milwaukee protocol and remained to survive for 15 days during the hospital stay but death occurred at home because of premature termination of treatment due to LAMA.

Rabies is a fatal disease accounting at least 60,000 deaths per year.[14] 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.[15] 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.[16] 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 ribavirin 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 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.

Table 2: A literature review of factors associated with good and bad prognosis in 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

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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