Abstract: Rabies is a fatal zoonotic disease spread through dog bites. Although post-exposure prophylaxis is known to offer complete protection, there are isolated case reports of disease occurrence despite vaccination. We report a case of a 20-year-old gentleman. He sustained a category 3 exposure on the upper limb following which he received 4 doses of purified chick embryo cell culture vaccine. However, the rabies immunoglobulin was not given. He presented with flaccid areflexic quadriparesis and absent brainstem reflexes 18 days following the exposure. He lacked the characteristic hydrophobia and aerophobia. Diagnosis of rabies was confirmed by the CSF antibody demonstration on RFFIT (rapid fluorescent focus inhibition test). The patient succumbed to the illness on day 25 following the dog bite. Paralytic variant of rabies is rare but described often in the setting of vaccine failure. Routine administration of rabies immunoglobulin in addition to vaccination is the key in prevention of vaccine failure.

Keywords: rabies, vaccine failure, antemortem diagnosis, paralytic variant

Introduction: Rabies is a zoonotic disease caused by an RNA virus belonging to family Rhabdoviridae and genus Lyssavirus. There are an estimated 20,000 new cases annually in India(1). The virus predominantly persists in the saliva of the infected animal and spreads through the nerves following animal bite. After entering the host it causes progressive encephalitis which is almost universally fatal(2). So far there have been very few human cases of survival resulting from a conservative strategy famously known as Milwaukee Protocol(3). Efficacy of post-exposure prophylaxis with human diploid cell vaccines has been well studied and is known to offer almost complete protection(4,5). Human diploid cell vaccine (HDCV) and Purified chick embryo cell vaccine (PCECV) is widely used in post-exposure prophylaxis. A recent CDC recommendation changed the five dose regimen to four dose regimen and eliminated the day 28 dose in view of lack of immunogenic response(6). We report a case of apparent failure of post-exposure prophylaxis despite vaccine administration as per recommended schedule. Case report A 20-year-old gentleman presented with sudden onset low grade fever, altered sensorium, urinary incontinence and rapidly progressive flaccid quadriparesis for 2 days. He had history of an unprovoked dog bite on the left third finger 18 days prior to onset of symptoms. Three other people were bitten on the lower limbs at the same time by the same dog. All four individuals went to a local hospital and were initiated on Rabipur (Purified Chick Embryo Cell Vaccine) and took four doses: 0, 3, 7, 14. At presentation he had tachycardia (HR 122/min) and tachypnea (RR 28/min) with shallow respiratory effort. There was flexor response to painful stimulus and no verbal response or spontaneous eye opening. His GCS at admission was E1 V1 M4 = 6/15. His pupillary light reflex and doll’s eye reflex were absent. Plantars were bilaterally extensor. He had terminal neck stiffness and flaccid areflexic quadriparesis. He had subungual hematoma on the left third finger at the bite site. Investigations showed leukocytosis with elevation in neutrophil counts (TC-25200, Neutrophils – 82%). His biochemical profile consisting of creatinine, liver function test, electrolytes and glucose were within normal limits. Cerebrospinal fluid analysis showed 230 cells with 66% polymorphs and protein of 72 mg% and sugars 57 mg%. The differentials of acute infective meningoencephalitis, post vaccine guillain barre syndrome, tetanus, botulism and substance abuse/toxicity were considered. An MRI of brain revealed patchy symmetric but subtle areas of long TR hyperintensities in bilateral basal ganglia, thalamus and cerebral peduncles along with Sulcal FLAIR hyperintensity in the fronto-parietal region bilaterally. The imaging features considered possible differentials of vaccine induced demyelination or viral encephalitis. In view of the poor neurological status shallow respiratory effort, he was intubated and mechanically ventilated. He was observed in ICU for 2 days with no change in the clinical status. Considering the history of dog bite, a possibility of paralytic rabies was considered. CSF was positive for Rabies antibody at a titre of 1:32 on RFFIT (rapid fluorescent focus inhibition test). Vaccine response seldom causes antibody production in the brain thereby suggesting a diagnosis of rabies(2). Family was counseled regarding the diagnosis and poor prognosis associated with it. To confirm the diagnosis of rabies, it was planned to repeat a CSF analysis after one week to document a rise in the titre of antibodies. The family however requested discharge against medical advice and took him to another hospital on day 5 of admission. The patient apparently died few hours following discharge and family was unwilling for post-mortem brain biopsy for confirmation of diagnosis.

Discussion: WHO classifies the rabies exposure into 3 categories(7). Category 1 involves licks of animals on intact skin and does not warrant any post exposure prophylaxis.
Category 2 involves bites resulting in minor scratches and abrasions, however, without bleeding. This warrants immediate wound cleansing followed by vaccination. Category 3 exposure involves transdermal or mucosal exposure and warrants Rabies Immunoglobulin (RIG) in addition to vaccination. The patient in our reference sustained a category 3 exposure and hence warranted RIG in addition to vaccination; however he did not receive RIG. Also there were three others who were bitten by the same dog at that time; however those bites were on the lower limbs on the thigh and these people remained asymptomatic. It is known that bites involving face, neck and arms are at a higher risk of disease compared to the bites on the legs.(8). Our patient was bitten on the terminal phalange which consists of multiple nerve terminals leading to the direct inoculation of the virus into the nervous tissue. This probably placed him at a higher risk than the others to develop rabies.

Rabies is most commonly known for classical symptoms of hydrophobia and aerophobia. These findings are seen in the encephalitis form of rabies which constitutes about 80% of all cases of rabies. Our patient however lacked these characteristic findings. There is also a less common paralytic form which fits in with our patient presentation. The paralytic form is more often associated with the vaccine failure and there are few case reports of the same(9–11). Antemortem diagnosis of rabies in most circumstances is based on the characteristic clinical features of hydrophobia and aerophobia in an appropriate clinical setting. Diagnosis of the paralytic form however remains a challenge in view of the various mimics. Polymerase chain reaction (PCR) of skin and saliva has very high sensitivity and specificity in diagnosis of rabies(12). Skin sample is recommended from the nape of the neck near the posterior hair line including some hair follicles(13). Detection of antibodies in the CSF is also reliable in antemortem diagnosis of rabies. Presence of antibodies in the serum can be resultant of immunization and hence not reliable for diagnosis of rabies. The best confirmatory test described for rabies remains postmortem brain biopsy which reveals negri bodies predominantly distributed in the hippocampus and basal ganglia region(2).

**Conclusion:** Category 3 exposure to rabies especially involving the face, neck or upper limbs result in the highest risk for transmission to rabies. The appropriate management in such cases is administration of RIG in addition to the vaccine. Although there are over half a million viats of RIG produced annually in India as per government statistics, their availability in most of the public sector health care facilities is low (14). It is also important to highlight the need for an efficient cold chain system to maintain vaccine efficacy especially in a tropical country like ours. Primary vaccine failure often presents as paralytic variant of rabies which mimics a myriad of clinical disorders. CSF antibody detection is widely available and can be used for antemortem diagnosis of rabies.

**Reference:**