

Case Report

An unusual case of fatal rabies encephalitis despite completing postexposure prophylaxis

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Abstract

Rabies continues to be a major health scourge in many developing countries including India. It can be effectively prevented by providing postexposure prophylactic treatment. Failure of Rabies postexposure prophylaxis (PEP) is a rare occurrence. Our patient, a 39-year-old Male, was bitten by stray dog on the left hand. It was Category III dog bite for which proper wound care and PEP 5 doses of antirabies cell culture vaccine and Human Rabies Immunoglobulin was given. Two days after completing the 5th dose of PEP, he presented with fever, neck rigidity, drooling of saliva, pain, and numbness in the left hand along with auditory and visual hallucinations without hydrophobia and aerophobia. On 2nd day of hospitalization, he developed progressive respiratory difficulty and decreased oxygen saturation for which he was intubated and put on invasive ventilator support. However, he suffered fatal cardiac arrest and succumbed to his illness. Based on his symptoms, a clinical diagnosis of febrile encephalopathy with differential diagnosis of acute rabies encephalitis was made. On autopsy, his brain was markedly congested and histopathological examination was suggestive of acute rabies encephalitis. However, no Negri bodies were seen. Further examination of brain tissue by immunohistochemical labeling revealed numerous Negri bodies and confirmed the diagnosis of rabies encephalitis.

Keywords: Encephalitis, failures of postexposure prophylaxis, postexposure prophylaxis, rabies postexposure prophylaxis, rabies

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INTRODUCTION

Since ancient times, rabies has been a major health scourge and still continues to do so mainly in the developing countries in Africa and Asia. Around 99% of human rabies is caused by Dog bite and the majority of them are stray dogs.^[1,2] In India, around 15 million people are bitten by dogs resulting in half of the rabies-related deaths worldwide.^[1,3,4] Preventive strategies for rabies include controlling the disease in the canine population and implementing effective

postexposure prophylaxis (PEP) guidelines recommended by the World Health Organization (WHO). Despite more than 10 million, suspected cases of rabies are given PEP annually, only sporadic cases of PEP failure have been reported which could be attributed to either deviation from WHO management recommendations and low potency biologicals (vaccine or immunoglobulin) or rarely, true PEP failure.^[2-6] Herein, we report a probable case of true PEP failure who developed acute rabies encephalitis

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despite completing WHO recommended proper wound care and PEP.

CASE REPORT

A 39-year-old Indian male patient presented with complaints of intermittent low-grade fever (100 F), myalgia, agitation, uneasiness and anxiety, drooling of saliva, the ringing of bells (auditory hallucinations), and visual hallucinations and tingling and pain and numbness in the left hand for the past 2–3 days after completing PEP course. One month back, he was bitten by stray street dog on the left hand which resulted in 2 cm × 1.5 cm lacerated wound (Class III dog bite). The same dog bit six other people nearby and not seen thereafter. After dog bite, the patient was managed as per the WHO guidelines by doing proper wound care and giving Intramuscular (IM) Purified Chick Embryo Cell culture vaccine (PCECV) type (Injection Rabipur, Chiron Behring Vaccines Pvt. Ltd., Mumbai, India) into Deltoid muscle (ESSEN Regimen, 0, 3, 7, 14 and 28 days) along with Human Rabies Immunoglobulin (RIG) 20 IU/Kg (Rabglob, Bharat Serums and Vaccines Ltd, India) was injected half into wound and half IM into the gluteal region within 6 h. On examination, he was restless, conscious, and oriented and his vitals were stable. Central Nervous Examination revealed neck rigidity. He was admitted with a provisional diagnosis of Encephalitis (Febrile Encephalopathy/Acute rabies encephalitis/). Complete blood counts showed polymorphonuclear leucocytosis while Cerebrospinal fluid examination revealed lymphocytic pleocytosis (Total cells-120 cells/cu mm, 70% lymphocytes, 30% neutrophils). Magnetic resonance imaging studies of his Brain showed bilateral symmetrical ill-defined area of signal changes in basal ganglia, hippocampus, midbrain, and patchy areas of signal changes in right thalamus suggesting the possibility of rabies encephalitis. On day 2 of hospitalization, he developed progressive respiratory difficulty and decreased oxygen saturation for which he was intubated and put on invasive ventilatory support. However, he suffered fatal cardiac arrest and succumbed to death. Based on his symptoms, a clinical diagnosis of febrile encephalopathy with differential diagnosis of acute rabies encephalitis was made and the autopsy was performed.

On gross examination, meninges and serial coronal sections of the brain showed multiple patchy congested area and subsequent histopathological examination of the cerebral cortex, cerebellum, hippocampus, and medulla revealed dense perivascular cuffing by lymphocytes and focal aggregates of polymorphs indicating acute viral encephalitis. However, no Negri bodies were seen [Figure 1]. However, further analysis of representative

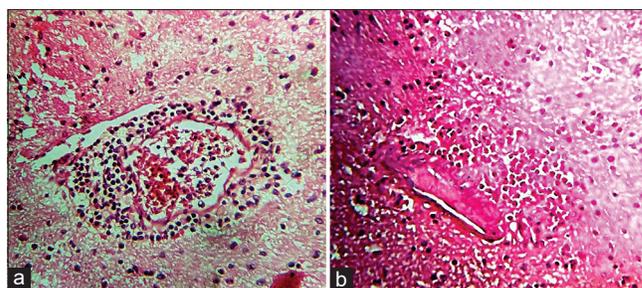


Figure 1: Histopathological examination of the brain revealed dense perivascular cuffing by lymphocytes and focal aggregates of polymorphs indicating acute viral encephalitis. However, no Negri bodies were seen (a and b: H and E, ×200)

brain sections by immunohistostaining using polyclonal antibody to Rabies (WHO Approved) at 1 in 10,000 dilutions with controls revealed numerous Negri bodies in small neurons. The lymphocytes were negative for the viral antigen. The histological features and immunohistostaining findings were confirmatory of acute rabies encephalitis.

DISCUSSION

Rabies, a viral zoonotic disease, is almost always fatal after the onset of clinical symptoms but paradoxically, 100% preventable too.^[1,2] Clinically, Human rabies can present either as encephalitic furious form (80% cases) or the paralytic dumb form (20%).^[3,5] Usually, encephalitic rabies presents with fever, agitation, pain, and paresthesia at the site of the bite, fluctuating consciousness followed by classical symptoms of phobic spasm-Hydrophobia (seen in up to 80% of patients) and Aerophobia along with autonomic dysfunction like increased salivation progressing to respiratory and bulbar paralysis and eventually, leading to death due to respiratory failure.^[3-5,7] Contrary to it, Paralytic rabies involve the spinal cord, clinically resembles with Guillion-Barre Syndrome, and rarely presents with classical symptoms of phobic spasm and autonomic symptoms.^[1,5] Our patient probably presented with encephalitic rabies, although hydrophobia and aerophobia were not present.

For the prevention of rabies-related mortality, it is essential to stop the spread of the virus from the site of inoculum. This is achieved by the WHO recommended protocols according to the category of the bite which includes proper wound management and PEP vaccination including RIG (RIG) to Category II and III bites. The vaccination status of the suspected case is also important. The most commonly used vaccine for PEP in India is Rabipur, a PCECV type of vaccine produced by using Low egg passage Flury rabies virus strain. WHO recommends two IM route and one intradermal (ID) route of vaccination regimen for PEP by using cell

culture vaccines having minimum vaccine potency of 2.5 International Units per dose.^[1,2] Over the last few years, the ID route is preferred over the IM route because of up to <80% dosage requirement and early formation of RNAb (7 days compared to 14 days with “gold standard” ESSEN regimen).^[2]

In deploying PEP, the immunization schedule should begin as soon as possible following exposure and must be followed exactly as recommended, regardless of when the patient comes in for treatment after the initial contact due to a prolonged incubation period varying from weeks to months. In individuals who have not been vaccinated with the rabies vaccine or individuals with uncertain immune status, Rabipur is administered via IM injection using the ESSEN five-dose regimen (one dose on Days 0, 3, 7, 14, and 28) or the Zagreb four-dose regimen (two doses on Day 0, followed by one dose on Days 7 and 21). In countries where the ID route of administration has been endorsed by national regulatory authorities, the WHO recommends the updated Thai Red Cross 2-site regimen (2 dose on 0,3,7 and 28 days).^[1] Immunocompetent cases who are previously vaccinated and show rabies-neutralizing antibody (RNAb) titers of at least 0.5 IU/ml should be given 1 dose of vaccine IM or ID on day 0 and 3 without any requirement of RIG.^[1] Vaccination schedule and dosage are identical in all individuals regardless of age, sex, and nutrition status.

Despite taking all precautions and giving PEP as per WHO guidelines, rare cases of PEP failure may to do occur and these can be attributed to [Table 1]:^[2-6,8]

Our case probably represents PEP failure because proper wound care and PEP was given from day 0 along with and Human RIG administration within 6 h of bite. However, The dog probably being rabid (as deduced from the history of the same dog biting six other people in the vicinity on the same day) and the large lacerated wound on hand, it is likely that a heavy viral load was introduced at the time of the bite. WHO recommends levels of RNAb ≥ 0.5 IU/ml at day 14 to assess the adequacy of PEP.^[2] Since levels of RNAb were not measured after 14 days of PEP in our case, another factor which may be attributable is improper and inadequate administration of PEP.

The burden of Rabies can be reduced in society by increasing awareness and following all instructions and guidelines for PEP. In 2012, the National Rabies Control Programme was launched in India as a part of the 12th Five-year Plan for the purpose of proper training and

Table 1: Probable causes of postexposure prophylaxis failure

Improper or no RIG administration in WHO Class II and III bites
Short incubation period
Inadequate knowledge about PEP at point of care
Failure to infiltrate maximum human RIG locally due to anatomic non feasibility and suturing of the wound
Poor availability and nonadherence to cold chain of costly cell culture vaccines and RIG in remote areas
Large viral inoculum directly at nerve endings usually on hand and face
Inadequate wound care
Inhibition of response of vaccine by antisera/immunoglobulin
Atypical virus strain resistant to RIG
Concurrent use of serum and antimalarials
Natural antibodies resulting from vaccination
Malnourished and immunocompromised patients, chronic diseases, alcoholism and drugs

PEP: Postexposure prophylaxis, RIG: Rabies immunoglobulin,

WHO: World Health Organization

implementation of PEP and also to strictly implement Animal Birth Control measures. The WHO in its global conference held in December 2015 have called for the elimination of “Dog mediated Human Rabies” by 2030 by adopting “One Health Approach” involving Medical, Veterinary, and other resources contributing to control and prevention of Rabies.^[9]

CONCLUSION

To conclude, classical signs of rabies-like hydrophobia and aerophobia may not be present in every case. Hence, proper care of the wound, use of proper dosage and schedule of rabies vaccine, and use of RIG as recommended by the WHO should be followed to avoid PEP failure and prevent Rabies-related morbidity and mortality.

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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