Magnetic resonance imaging abnormalities in encephalomyelitis due to paralytic rabies: A case report

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Abstract
The diagnosis of rabies, a potentially fatal neuroinfectious disease, should be strongly considered in all patients who develop encephalitis following an infected animal bite even when they have received post-exposure prophylaxis. In the absence of confirmatory tests, typical magnetic resonance imaging findings help confirm the clinical diagnosis of rabies.

KEYWORDS
encephalomyelitis, magnetic resonance imaging, paralytic rabies

1 | INTRODUCTION

Rabies is a fatal viral disease caused by a bullet-shaped ribonucleic acid lyssavirus belonging to the family Rhabdoviridae.1 Ninety-five percent of the human cases of rabies worldwide are transmitted by dog bites, this figure reaches 99% in endemic regions.2 Infected animals transmit the virus to other animals and humans through their saliva.3 The infection localizes in the central nervous system resulting in encephalitis and encephalomyelitis and has fatality rate of almost 100%.4 Although the incidence of rabies is decreasing worldwide, thanks to very effective pre- and post-exposure prophylaxis, it is estimated that one person dies from rabies every 10–20 minutes among population in endemic regions of the world.4 According to the reports published by a dedicated infectious disease hospital in Nepal, around 150 people visit the hospital each day to receive anti-rabies vaccine.5 Up to 32 human deaths have been reported in Nepal due to rabies in the last five years.6 The diagnosis of rabies can be confirmed by laboratory tests, but such tests are often not available in resource-limited settings.7 Typical magnetic resonance imaging (MRI) findings can help confirm the clinical diagnosis of rabies in appropriate clinical context.8-12 In this article, we report a case of a young male with paralytic rabies who presented with clinical and magnetic resonance imaging features of acute and rapidly fatal encephalomyelitis following a dog bite despite having received post-exposure prophylaxis.

2 | CASE PRESENTATION

A 17-year-old man from a remote village in Nepal presented to the emergency department of our university...
hospital in Kathmandu with high-grade continuous fever of four-day duration. At presentation, the patient had urinary retention and was unable to move bilateral lower extremities for two days and was having an altered level of consciousness for one day. Per report, he did not have headache, vomiting, seizures, or any abnormal bodily movements. A month prior to onset of his symptoms, he had been bitten by a stray dog, on his left leg and hand. The dog reportedly escaped and its whereabouts was not known. The patient had received four doses of purified chick embryo cell inactivated rabies post-exposure vaccine—the last dose about five days prior to presentation to our center. It was not known whether rabies immunoglobulin was administered. On examination, he was restless and not oriented to time, place, and person. His Glasgow Coma Scale score was 11/15 (E4M5V2). He had neck stiffness. His pupils appeared normal but oculocephalic reflexes were absent. Other cranial nerve examination was intact. The patient did not have features suggestive of hydrophobia. His limbs were spastic with exaggerated deep tendon reflexes and extensor plantar responses bilaterally. Based on the antecedent history of dog bite followed by neurological symptoms and signs, a provisional diagnosis of paralytic rabies with encephalomyelitis was made.

His complete blood counts and comprehensive metabolic panels were unremarkable. The magnetic resonance imaging (MRI) of the brain and the whole spine which was done on the sixth day after the onset of symptoms revealed T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensities in the dorsal medulla, dorsal pons, dorsal midbrain, hypothalami, and the whole of the spinal cord (Figures 1–5). Lumbar puncture revealed 70 nucleated cells (96% lymphocytes) with normal glucose and protein levels. The cerebrospinal fluid (CSF) was sent for polymerase chain reaction (PCR) study for neurotropic viruses including rabies virus reverse transcriptase PCR (RT-PCR). The results were negative. Serum antibody tests for Japanese encephalitis were also negative. Electroencephalogram (EEG) could not be done as the patient could not be transferred for the test, and bedside EEG was not available at that moment.

The patient required intubation and mechanical ventilation on the sixth day into the illness. Because of the remote possibility of vaccine-induced encephalomyelitis and other demyelinating diseases of the central nervous system, he was also treated with high dose intravenous methylprednisolone. His family, however, could not afford plasma exchange and intravenous immunoglobulins. CSF studies for rabies antibody and skin punch biopsy from the nape of the neck were planned but could not be done as those tests were not available. Despite aggressive supportive care, he lost all his brainstem reflexes over the next five days and passed away on the eleventh day of his illness. The characteristic clinical presentation of this patient on the background of antecedent dog bite, the rapidity of progression of the illness to death and the typical imaging findings all were highly suggestive of rabies encephalomyelitis and the final diagnosis of the same was made. Autopsy was not requested because of social and cultural reasons.

3 | DISCUSSION

Rabies is a fatal zoonotic disease and is maintained in most parts of the world by dogs, foxes, raccoons, mongooses, and skunks. Rabies is also maintained in multiple bat species in the Americas. The main mode of transmission of rabies is through bite of an infected animal; other rare modes of transmission include organ transplantation and aerosols.

Once rabies virus enters the host, it travels to the central nervous system and preferentially affects the bulbar and limbic areas. The pathological changes are evident in the form of an encephalomyelitis occurring predominantly in the gray matter of the brain and the spinal cord. Although present only in 50–80% of cases, the pathognomonic histological feature of rabies is the presence of Negri body, which is an eosinophilic intracytoplasmic inclusion body.
striking pathologic changes are seen in the gray matter of the spinal cord, in addition to the changes in the gray matters of the cerebrum and the brainstem.\textsuperscript{16}

FIGURE 2  FLAIR MRI image of the patient showing hyperintensity in dorsal pons (white arrow)

The incubation period of rabies varies considerably and most patients develop symptoms 20–90 days after exposure.\textsuperscript{4} Based on the clinical manifestations, rabies is divided into two classical types: furious (also called encephalitic) and dumb (also called silent or paralytic).\textsuperscript{7} The majority of patients (80\%) with rabies exhibit signs and symptoms of encephalitic form and about only 20\% exhibit clinical features of the paralytic form.\textsuperscript{16} The paralytic form has mostly been described in patients who develop the disease despite having received post-exposure prophylaxis.\textsuperscript{9} Initial symptoms of rabies consist of pain, paresthesia and/or pruritus at and around the site of the bite.\textsuperscript{17} The neurological phase of the disease, which manifests after a few days, is characterized by typical clinical manifestations.\textsuperscript{7} Furious rabies presents during this phase with agitation, hypersalivation, dysautonomia, hydrophobia, and aerophobia, the latter two symptoms are very specific to rabies.\textsuperscript{7} The paralytic form, on the other hand, presents with progressive limb and eventually bulbar muscle weakness.\textsuperscript{7} Both forms eventually culminate into coma and, almost universally, death.\textsuperscript{4} Although most patients with paralytic rabies present like Guillain-Barré syndrome with flaccid paralysis, spastic quadriparesis, as in our patient, has been described in a case report.\textsuperscript{12} Rapid onset and progression of symptoms and signs of encephalomyelitis after the dog bite in our patient is highly suggestive of rabies and as published in a case report, our patient with paralytic rabies developed symptoms despite post-exposure prophylaxis.\textsuperscript{9}

FIGURE 3  FLAIR MRI image of the patient showing hyperintensity in dorsal midbrain (white arrow)

FIGURE 4  FLAIR MRI image of the patient showing hyperintensity in bilateral hypothalamus (white arrow)
The diagnosis of rabies is suggestive when a patient presents after being bitten by a potentially rabid animal. Ante-mortem diagnosis is made from samples obtained from nuchal skin and saliva. Immunofluorescence staining for viral antigen in skin specimens and RT-PCR test in both skin and saliva can be carried out to confirm the diagnosis. Detection of the virus-specific antibodies in the serum of unvaccinated individuals, or in the CSF of both vaccinated and unvaccinated individuals, is also highly suggestive of the diagnosis. Post-mortem diagnostic tests are carried out in the brain tissue. As stated earlier, the pathognomonic histologic feature of rabies is the presence of Negri bodies. The gold standard diagnostic test, recommended by both World Health Organization and World Organisation for Animal Health (OIE), is a direct fluorescent antibody test (dFAT) to detect virus antigen in brain impressions. In our patient, only CSF was tested with rabies virus RT-PCR which turned out to be negative. Negative PCR by itself could not rule out rabies as the sensitivity of RT-PCR to detect rabies virus nucleic acid in CSF is very low. As discussed in the case presentation, CSF studies for rabies antibody and skin punch biopsy from the nape of the neck were planned but could not be done as those tests were not available. Saliva, however, was not sent for RT-PCR.

In the absence of PCR, antigen and serological tests, imaging studies can be of great value in supporting a diagnosis of rabies. Early in the disease, imaging can be normal which may be followed by evidence of cerebral edema in both computed tomography and magnetic resonance imaging of the brain. MRI picture of brain and spinal cord of patients with rabies can be very characteristic with predominant involvement of gray matter considered hallmark of the disease and thus differentiating it from acute disseminated encephalomyelitis which predominantly involves the white matter. Multiple case reports have discussed that the evidence of rabies encephalitis is seen as high signal intensity on T2 and FLAIR MRI sequences in bilateral hippocampi, thalami, basal ganglia, and dorsal aspect of brainstem and can be very specific to rabies in appropriate clinical context. Pathologic studies and immunohistochemistry tests carried out in deceased individuals with rabies have also shown maximal concentration of Negri bodies and viral antigens in these areas. Even though we could not carry out confirmatory tests in our patient, the MRI findings of our patient were similar to the ones described above and provided a strong evidence—in the clinical context of rapidly progressive fatal disease following stray dog bite—of rabies in our patient.

Rabies is well preventable with prompt post-exposure prophylaxis. Unfortunately, prophylaxis failures do occur most often because of deviations in recommended standard protocols. Other reasons behind post-exposure prophylaxis failures are delay in seeking treatment, improper wound care, lack of or incorrect rabies immunoglobulin administration, inadequate vaccine doses, and very rarely from the use of substandard products. Very rare reports of patients who develop fatal rabies despite having received adequate post-exposure prophylaxis are attributed to short incubation periods in someone who has sustained multiple bites, especially on highly innervated areas such as the face, neck or hands. Our patient had also sustained multiple bites in leg and hand.

FIGURE 5 Sagittal T2 MRI image of the patient showing hyperintensity extending from the whole of the posterior brainstem to the central gray matter of the entire spinal cord (white arrows)
All licensed vaccines against rabies are considered to be very safe. Rare case reports of neurologic adverse events such as acute disseminated encephalomyelitis and Guillain-Barré syndrome following rabies vaccination have been reported. However, mortality following licensed rabies vaccine administration has not been reported. Vaccine-induced neurological side effects could be a possibility in our patient. However, typical MRI findings and severe encephalomyelitis which was rapidly progressive and fatal within a few days of onset despite high dose intravenous methylprednisolone are highly suggestive of a diagnosis of rabies in our patient.

4 | CONCLUSION

This case illustrates that the diagnosis of rabies is possible in a patient even when the patient has received post-exposure prophylaxis following a potentially rabid animal bite and thus requires a high index of suspicion. Rabies presents with acute onset and rapid progression of symptoms and signs of encephalomyelitis and is rapidly fatal due to the lack of any definitive curative treatment. Although demonstration of rabies virus nucleic acid in saliva, Negri bodies in skin or brain specimens and viral antigens in pathological specimens are considered confirmatory, typical magnetic resonance imaging evidence of involvement of posterior brainstem, hypothalamus, thalamus, and gray matter of the spinal cord can provide a strong evidence of infection with rabies virus in appropriate clinical setting.

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CONFLICTS OF INTEREST

The authors do not have any conflicts of interests.

AUTHOR CONTRIBUTIONS

All the authors have contributed equally to conception, design, manuscript preparation, critical revision, and finalization. All the authors agree to be accountable for all aspects of the work.

ETHICAL APPROVAL

Ethical approval was not required for the publication of this report.

CONSENT

Written informed consent was obtained from the father of the patient to publish this report in accordance with the journal’s patient consent policy.

DATA AVAILABILITY STATEMENT

The details supporting the information in this manuscript can be made available from the corresponding author upon request.

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