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Case Report

Atypical paralytic rabies — A case-study from Kerala, India

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ABSTRACT

Introduction: Rabies, though endemic in India, has been a disease of low public health priority throughout the years. Being a non-notifiable disease together with limited diagnostic facilities, it often ends up in under-reporting of cases, especially atypical rabies. Failure of complete rabies Post Exposure Prophylaxis (PEP) with Immunoglobulin has been rarely reported.

Case: We report a case of atypical rabies in a 60-year-old man from a rural village in Kerala, who presented with fever, paralysis of limbs, fluctuating consciousness, phonophobia and without classical signs of hydrophobia and aerophobia 22 days after dog bite. The case is supplemented with supportive Magnetic Resonance Imaging (MRI) findings and corneal imprint smear Fluorescent Antibody Test (FAT). The death of the patient on the 28th day of exposure despite early PEP with rabies vaccine and immunoglobulin is suggestive of PEP failure.

Conclusion: The case study stresses on the need in making rabies a notifiable disease in the study setting, encouraging disease specific investigation, ensuring availability of vaccine and immunoglobulins with adherence to standardized treatment protocols.

Key Messages: Deviations from the recommended protocol for Animal bite management, such as delay in seeking PEP, lack of or improper administration of rabies immunoglobulin (e.g. missing out bite sites), lack of or improper primary wound care, and/or poor-quality rabies vaccine, may lead to death.

1. Introduction

Rabies, though endemic in India, has been a disease of low public health priority throughout the years. Being a non-notifiable disease together with limited diagnostic facilities, it often ends up in under-reporting of cases, especially atypical rabies. Failure of complete rabies Post Exposure Prophylaxis (PEP) with Immunoglobulin has been rarely reported.

On 24^{th} May 2015, a family came to the Out Patient Department (OPD) of Preventive Medicine of our institution for taking Post Exposure Prophylaxis (PEP) against Rabies. The reason was that the head of their family died earlier that day suspected of rabies. It was found that the man who had died, had been bitten by his pet dog and had taken PEP as both Intra-Dermal Rabies Vaccine (IDRV) on days 0, 3, 7 and wound site infiltration of Equine Rabies Immunoglobulin (ERIG). The man died on the 28^{th} day of exposure in spite of all the preventive measures.

2. Case History

A 60-year-old man previously fit and well, from a remote village in Kerala, was bitten by his pet dog on 26^{th} April

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2015. The dog had been with the patient for the past 12 years, it was immunized against rabies once 8 years back. Though the house lacked a compound wall, the dog was neither caged nor locked, but was kept free and mostly it stayed within the premises. The dog was apparently normal until that day, when it bit the patient, and a neighbour. The bite was a provoked one, on the left thumb, with significant bleeding. The wound was immediately washed with soap and water and PEP (IDRV D0) was taken from the District Hospital approximately after four hours. ERIG was not available at the District Hospital and he was referred to the next higher centre for it. The patient came back home without taking ERIG and was again bitten by the same dog, this time on his left forearm. The wound was washed with soap and water. The dog was killed by the neighbours later that night; however no pathological samples could be collected at that time. On the next day the patient went to a higher centre (General Hospital), where he was tested for sensitivity for ERIG which is a prevalent practice in Kerala.[1,2] Sensitivity testing is done by injecting 0.1ml of ERIG in 1:10 dilution intradermally into the flexor aspect of forearm to raise a 3-4mm bleb, the injection site is marked and observed for a period of 15minutes for occurrence of induration >10mm,surrounded by flare, an increase or abrupt fall in blood pressure, syncope, or any systemic manifestations.[1,2] The patient was found to be sensitive for ERIG. He was then referred to a tertiary care referral centre. However ERIG could be taken from the tertiary care centre (Medical College) only on the second day. It was taken after administering steroid and antihistamine injections to reduce sensitivity. Human Rabies Immunoglobulin (HRIG) was not given instead of ERIG because it was not available in regular Government supply and was too costly for the patient to buy from outside. Thereafter, the patient had taken remaining doses of PEP (IDRV D3 and D7) on the scheduled days from the District Hospital. He had been healthy and physically active throughout this period.

However, on the 22^{nd} day of exposure the patient developed fever and vomiting. He became anxious and apprehensive, developed a disliking for loud noises and preferred to remain indoors most of the time. He was treated in a local Primary Health Care Centre with anti pyretic and anti emetic medications. Two days later, he had pain and swelling all over the injured forearm and hand. On the 25^{th} day he developed slurring of speech, imbalance while walking and weakness of left side of the body. He was anxious and irritable by that time. By night the weakness extended to the right side of body. He was taken to the District Hospital where he was managed with intra venous fluids and injection Mannitol. Computerized Tomography (CT) of the head performed was normal, with no evidence of intracranial haemorrhage, space occupying lesion or ischaemic foci and hence the patient was referred to the tertiary care referral centre (Medical College).

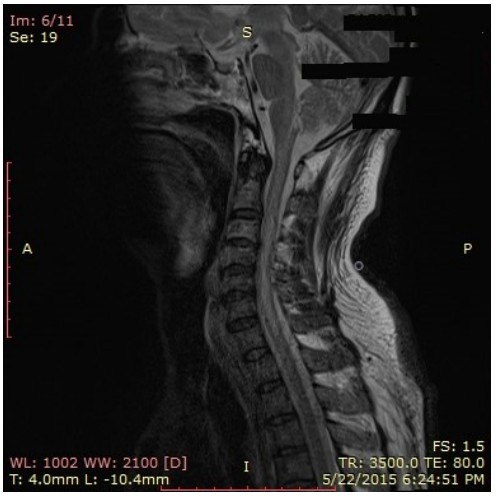

Fig. 1:

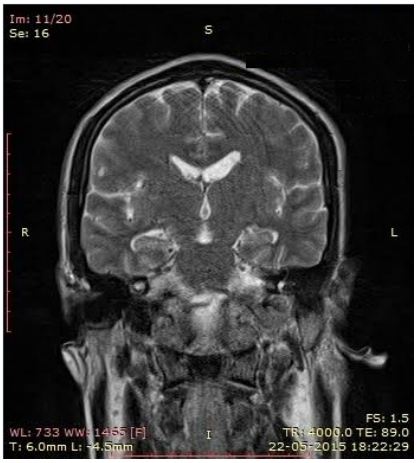

Fig. 2:

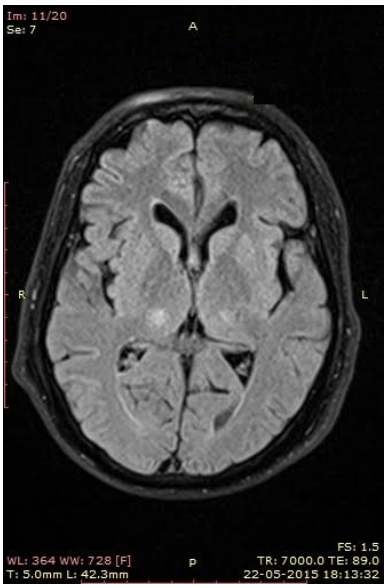

Fig. 3:

In the tertiary care centre, he was assessed to be conscious, disoriented and in delirium, with diaphoresis, dysarthria and phonophobia. His heart rate was 80 beats /minute, regular and blood pressure 120/80mm Hg. Respiratory and cardiovascular system was normal and there was no organomegaly. His pupils were sluggishly reactive and had grade 0 power in both upper limbs and grade 4 power in both lower limbs. The plantar reflex testing showed a flexor response bilaterally. The haematological, renal, hepatic parameters, electrolytes, and blood glucose values were normal. He was admitted and subjected to a detailed neurologic examination. The duty neurologist examined the patient the next day morning and reported slightly different clinical findings. The patient was conscious and was obeying commands at that time. He was having severe dysarthria and hypophonic speech. There was no evidence of hydrophobia or aerophobia. Bilateral gaze evoked nystagmus was present. There was hypotonia in both upper limbs whereas both the lower limbs had normal tone. Quadriparesis was present with grade 3power in both lower limbs and grade 3 and grade1 power in right and left upper limb respectively. Plantar reflex testing showed equivocal response in left side and a flexor response in the right side.

Magnetic Resonance Imaging (MRI) of the brain was done. The radiologist reported T2 weighted and Fluid Attenuation Inversion Recovery (FLAIR) images of hyperintense lesions in the dorsal medulla, dorsal pons, tegmentum of midbrain (Figure 1), hippocampi (Figure 2) and bilateral thalami (Figure 3). Screening of cervical spine showed heterogeneous hyperintense lesions in the cervical spinal cord involving more than 2/3rds of the circumference of the cord, with mild cord enlargement (Figure 1). According to the radiologist, the areas of brain involved were typical of Rabies Corneal impression smears were sent for Fluorescent Antibody Testing to Rabies Diagnosis Laboratory, Chief Disease Investigation office, Palode. They reported that a few fluorescent particles were detected in one smear. However, the salivary and hair follicle sample study advised by the neurologist could not be done. The patient was managed symptomatically, supportive treatments were given but he deteriorated on the second day of admission and succumbed early morning next day, the 28^{th} day of dog bite. Post mortem examination was not performed.

3. Discussion

The suspected rabies infection reported here was contracted from a partially vaccinated, unchained dog which was killed without being subjected to any pathological tests. In India, the major chunk of the disease transmission occurs through dogs (91.5%). In India, 76% of rabies cases were reported from rural communities[3] where no dog vaccination programmes have been conducted at large scale, and thus the incidence of dog rabies presumably remains high. There is no effective policy for control of canine population or their vaccination in this setting. It has been a proven that control of canine rabies is achievable through a sustained canine vaccination coverage of 70%[3–10] along with stringent measures for stray dog control.

The patient was given prompt intra-dermal PEP. Immunoglobulin was delayed as the patient was sensitive to the ERIG. HRIG was not attempted as the patient could not afford the drug, and ERIG was the only drug available in free governmental supply. Many studies have shown that there is a lacuna in awareness regarding the disease, its prevention and treatment guidelines even among the medical professionals.[11–13] The economic constraints and lack of appropriate legislative measures have led to an irregular supply of anti-rabies vaccine and immunoglobulin, especially to the primary care hospitals. Intradermal vaccine for low resource settings has been practiced extensively throughout Government Hospitals in Kerala since 2008.[14] However, the intradermal vaccination technique requires special training for the health care providers, in order to reduce the risk of insufficient dosing.[15]

Human rabies may present in two clinical forms, namely encephalitic (furious/classic) in 80% cases and paralytic (dumb) in 20% cases.[16] The varied clinical picture in two forms is attributed to the difference in site specific responses: in encephalitic form, the brain stem, cerebrum and limbic system are involved, whereas in paralytic form, medulla and spinal cord are mainly involved. Basal ganglia and thalamic involvement are seen later in the course of the disease.[17] The patients are often alert with intact cognition, but with notable behavioural and emotional changes that can be correlated with localization of the virus in the limbic system and with a cortical sparing.

On the 22^{nd} day after the bite, our patient developed nonspecific/prodromal symptoms of encephalitis like fever, malaise and vomiting, which were subsequently followed by pain and swelling of the affected forearm. In about 50% cases of paralytic rabies and 30% cases of furious rabies local manifestations like itching, paresthesia or pain at the bite site may be the initial symptom,[16] which are often neglected by the patients and may later involve the entire bitten extremity as would have happened in our case.

Neurological phase develops within hours or a few days after the prodrome. About 80% of the patients suffer an encephalitic (furious) form while the rest present as paralytic form. The latter lacks the classical symptoms of rabies and is often mistaken for acute disseminated encephalomyelitis (ADEM) or acute inflammatory demyelinating polyneuropathy.[18] Nervousness and hyperactivity, often associated with moderate to high grade fever, are the earliest manifestations in furious rabies. The case described here was atypical in its neurological presentation. Our patient had neurologic symptoms like irritability and mood swings on the first day of symptoms.

Table 1: Featuresused to differentiate between furious rabies and paralytic rabies in comparison with observations in the case under study

Characteristic feature	Furious rabies	Paralytic rabies	Our case
Incubation period (usually 20-90 days, extreme range 4days -20 years)	Short, usually days	Longer, weeks/months	22days
Development of prodrome (usually 2-10 days) Fever, malaise, anorexia, nausea, vomiting, paraesthesia and pain or pruritus at the wound site are the usual symptoms	Reported in 50% cases	Reported in 30%cases	3days of Fever, vomiting, pain and swelling of injured arm
Acute neurologic disease	Usually Encephalitic, found in 80%	Usually Paralytic, found in20%	Reported, predominantly paralytic
Symptoms and signs	Anxiety, agitation, hyperactivity, bizzaire behaviour, hallucinations, autonomic dysfunction, hydrophobia, etc	Flaccid paralysis in limb(s) progressing to quadriparesis with facial paralysis	Slurring of speech, imbalance on walking, ascending flaccid paralysis progressing to quadriparesis, anxiety, fluctuating consciousness, phonophobia, dysarthria and diaphoresis
Vaccination status	Usually unvaccinated	Proportion of partially vaccinated cases are more	Fully vaccinated with immunoglobulin
Coma and Death	Rapid, usually within 7 days of clinical disease	In most of the cases 7-11 days of clinical disease	Death occurred at 7^{th} day of the start of clinical manifestations
MRI	No specific features of demarcation. However, some studies report more involvement of spinal cord and medulla in case of paralytic rabies		Generalised brain involvement with that of spinal cord

He had phonophobia, whereas the classical symptoms like hydrophobia or aerophobia were absent. He was conscious initially, but later showed diminished attention span, irrelevant speech, fluctuating consciousness and signs of autonomic dysfunction like diaphoresis. As observed in cases of paralytic rabies, the patient had weakness in the bitten extremity initially, which later evolved into a descending flaccid paralysis. The flaccid paralysis was similar to that in Guillain Barre Syndrome and Cardiovascular accident, posing diagnostic difficulty.

The pathogenetic basis for two clinical forms of rabies is not known. No difference with respect to the viral strains, incubation period or the site of bite has been observed among the two forms. However, paralytic rabies is attributed to the immunopathological attack on the virus infected cells of the brain and spinal cord. It is also postulated that paralytic rabies usually occurs in people who have received incomplete/ineffective immunization,[16–20] as in the case under study.

Radiological diagnosis of rabies has not been studied in depth, as the disease has a rapid clinical course with usually hard-to-manage patient, making neuro-imaging difficult.[21] CT scan is usually less sensitive,[22] as in our case. In MRI, abnormal, ill-defined, increased T2 signal with a predilection for the basal ganglia, thalami, hypothalami, brainstem, limbic system and spinal cord is indicative of diagnosis of rabies, irrespective of clinical types.[4] This correlates with the MRI findings of our patient, with overlapping involvement of areas described in classic and paralytic forms. The areas of brain involved were typical of rabies, in contrast to other viral encephalitides and ADEM. Even though MRI is not performed for routine diagnosis of rabies, it may prove useful as an additional tool for early diagnosis of rabies encephalitis,[18,20,21] as in our case where the clinical symptoms were not typical. The features that help to differentiate between furious and paralytic forms of rabies, based on our literature search is given in Table 1.

Diagnosis of rabies made on clinical grounds alone is often unreliable. Confirmation of clinical cases of rabies is through laboratory-based techniques. Fluorescent Antibody Testing recommended by WHO gives reliable results in 90-95% of cases, if done on fresh specimens within a few hours. All biological fluids (saliva, spinal fluid, tears) and tissues (skin biopsy samples and hair follicles at the nape of the neck) can be used for ante mortem rabies diagnosis. The most sensitive samples include three saliva samples taken at intervals of 3–6 hours, and samples of skin and hair follicles.[4] Even though these tests were ordered, they could not be carried out due to demise of the patient on the second day of admission. The corneal imprint smear of the patient was sent and a few fluorescent particles could be seen. However, a conclusive result was not obtained, possibly due to inappropriate sample or minimal viral load in the sample specimen.[3–25] Post mortem confirmatory tests were not done as no facilities were available in our setting for

performing pathological autopsies for such highly infectious diseases.[8–26] Thus, the patient described herein is as an atypical probable case[4] of paralytic rabies, with supportive MRI features.

The unavailability of HRIG in public system and financial constraints to purchase it, added on with an allergy to ERIG test dose often end-up in delayed immunization. The summation of these factors might have attributed to the ineffective immunization in our case. There is a possibility that the steroid used for de-sensitisation might have delayed immune response in our case.[27–30] Deviations from the recommended protocol, such as delay in seeking PEP, lack of or improper administration of rabies immunoglobulin (e.g. missing out bite sites), lack of or improper primary wound care, and/or poor-quality rabies vaccine, may lead to death.[4] The facilities for investigation of a clinical case of Rabies should be standardized in the study setting and the clinicians should be trained and motivated to investigate a Rabies case scientifically. This culture may be built for all Neglected Tropical Diseases. Facility for pathological autopsy should be established for similar cases. Rabies must be declared a notifiable disease and stringent measures for adherence to the same must be ensured at all levels by the health authorities.

4. Source of Funding

None.

5. Conflict of Interest

None.

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