

Review Paper

Rabies Virus Infection: A Case Series and Literature Review



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ABSTRACT

Background: Rabies is a fatal and often neglected disease leading to encephalomyelitis following a bite by an infected mammal. According to the necessity of rabies disease in Iran, we present four cases of rabies virus infection.

Case Presentation: We presented 4 cases of rabies virus infection hospitalized in different hospitals in Iran in 2021-2022. Three patients were male. The youngest patient was 6 years old and the oldest was 81 years old. In all 4 cases, RT-PCR detected the positive virus infection. Three cases received rabies immunoglobulin. All of them received at least one dose of rabies vaccination; but, unfortunately, all patients died.

Conclusion: The present case series showed the necessity of early rabies vaccination and also the early organization of stray dogs in the community. Unfortunately, two cases were lost to follow-up. So, the population education and follow-up of suspected rabies patients must be taken seriously by healthcare facilities.

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Introduction

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abies is a fatal and often neglected disease leading to encephalomyelitis following a bite by an infected mammal [1]. Rabies infection is classified as furious and paralytic. Furious rabies manifests with mental status fluctuation, phobic or inspiratory spasms, and autonomic stimulation signs.

Paralytic rabies inflames the spinal cord and induces necrosis. Guillain-Barré syndrome, coma, and myoedema are all symptoms of this rabies [2]. Based on the results of the study conducted in Mazandaran province, the average frequency of animal bites was 3174 to 4670 cases per year [3]. According to the necessity of rabies disease in Iran, we present four cases of rabies virus infection.

Case Presentation

Case 1

A 6-year-old boy was admitted to a referral hospital with a chief complaint of fever, decreased Level of Consciousness (LOC), and status seizure that had been controlled with anticonvulsant medications. He had no history of the disease. He was intubated and underwent mechanical ventilation. In the physical exam, the scar of the suture following a stray dog bite one month ago was observed. The history showed that a single dose of delayed rabies vaccination had been administered. The cause for losing follow-up is unknown. The rabies vaccination (first, third and seventh days) and rabies immunoglobulin (first day) were administered immediately. The LOC decreased after 10 days of hospitalization and the sedation drugs had been held. The laboratory data were abnormal urea (BUN=229 mg/dL), creatinine (Cr=2.8 mg/dL), LFT (ALT=711 u/L, AST=841 u/L), and high creatine phosphokinase (CPK=4305 u/L), and sodium (Na=155 mEq/L) levels. Finally, renal failure occurred. After a positive rabies salivary reverse transcriptase-polymerase chain reaction (RT-PCR), IVIG 1 gr/kg was discontinued, and rabies vaccination and immunoglobulin were prescribed (Table 1). Unfortunately, he died 18 days after admission.

Case 2

A 47-year-old man was admitted with a chief complaint of loss of appetite and hydrophobia four days before hospitalization and spasms of the extremities on admission day. He implied contact with a domestic dog one week before admission, but the physical exam showed no lesions following the dog bite. He received

rabies vaccination on the first and third days of hospitalization, but he did not receive rabies immunoglobulin. During hospitalization, the patient was agitated, so the psychiatric consult requested an IV diazepam PRN (up to four times a day) be prescribed. However, this symptom was not controlled and haloperidol and biperiden were prescribed. Due to the positive rabies salivary RT-PCR, rabies vaccination was administered. Also, the family reported a history of pre-exposure rabies vaccination but the time of the last vaccination was unknown. Four days after admission, he suddenly showed dyspnea, so he was transferred to the ICU and intubated. On the same day of the ICU admission, the heart rhythm changed to sinus bradycardia and cardiac arrest occurred. Finally, he died.

Case 3

A 13-year-old boy was admitted with a chief complaint of headache (one week before hospitalization), agitation, and restlessness (three days before hospitalization). In the physical exam, proptosis eyes, mydriasis, photophobia, hydrophobia, normal gag reflex, normal cranial nerve, and extremity tonicity 5/5 were observed (Figure 1). He had a history of fox scratch with bleeding two months ago. But the reason for the referral to the healthcare setting was unknown. Baseline laboratory data showed leukocytosis (WBC=19700 per microliter) with lymphopenia (lymph=7%). Sedative medication was prescribed to manage the agitation. At 14 hours after hospitalization, the gag reflex disappeared and the patient showed dysarthria. The last physical exam showed flaccid with generalized areflexia. The CSF and salivary RT-PCR showed positive rabies infection. So, a single dose of rabies vaccination and immunoglobulin was administered. Unfortunately, according to the clinical outcome of the patient, he was intubated and supportive mechanical ventilation was performed; but, he died 24 hours after admission.

Case 4

An 81-year-old woman was admitted with a chief complaint of loss of appetite, weakness, and ataxia (3 days before admission). Baseline laboratory tests were normal. In the physical exam, the scar following a stray dog bite was visible. She had a history of stray dog bite 17 days before admission and she had received a four-dose rabies vaccination and immunoglobulin. The first dose of the rabies vaccine was administered immediately on the same day of the dog bite. Accordingly, CSF and salivary RT-PCR for rabies virus were requested and the results showed positive rabies infection disease. At 24



Figure 1. The proptosis eyes in patient

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hours after hospitalization, the oxygen saturation decreased and so they were intubated. However, cardiac arrest occurred 48 hours after admission and she died.

Discussion and Literature Review

Epidemiology in Iran

In general, the incidence rate of animal bites in Iran was 13.20 per 1,000 people. Also, the highest incidence rate of animal bites was reported in West Azarbayjan Province (146.83/1000) in the northwest of Iran. The mean age of rabies infection was 26.23 years old. Furthermore, the male and female incidence rates per 1,000 populations were 14.9 and 4.55, respectively. The incidence rate in rural areas was higher than in urban areas (17.45 vs 4.35 cases per year) [4]. According to the Pasteur Institute report, the mortality rate of rabies is 5 to 11 people annually [5]. Dog bite accounts for 81% of all rabies infection reports in Iran [6]. Other animal hosts for this disease include foxes, jackals, and wolves [7, 8]. The incidence rate of incomplete vaccination was higher than the complete vaccination (11.8 vs 3.65 per year) [4].

Pathogenesis

When the rabies virus enters the body through a skin breakdown, it replicates in muscle cells and then infects the muscle spindle and the nerves that innervate them and move centrally. Rabies infection proliferates within the CNS and is centrifugally spread via the peripheral nerve to the rest of the tissues [9]. The immune response of the body to rabies infection is insufficient. The rabies infection can produce immunosuppression due to interleukin-1 production in the CNS. Some believe that the virus may persist in macrophages and emerge late after the infection. It accounts for long incubation periods in some cases [10, 11].

Clinical manifestation

Some variables affect the risk and the rate of rabies infection development after exposure, including viral

inoculum, the number and location of the bites, and a preexisting wound. As mentioned earlier, rabies virus infection is classified into two categories: Furious rabies (encephalitic) and paralytic rabies (dumb). The pathogenic distinction between them is unclear. The most common symptom of furious rabies is hydrophobia. Other symptoms are episodic hyperactivity, seizures, aerophobia, hyperventilation, pituitary dysfunction, cardiac arrhythmias, and autonomic dysfunction. Paralytic rabies is manifested by ascending paralysis, hypophonia, acute inflammatory polyneuropathy, symmetric quadriparesis, and weakness [12, 13].

Diagnosis

During the incubation period, diagnostic studies are useless. Also, when the symptoms appear, standard laboratory testing is not reliable in terms of distinguishing rabies from other encephalitis. Direct fluorescent antibodies (DFA) of biopsy or necropsy tissue are a standard diagnostic test. DFA detects the presence of rabies virus antigen [14]. The RT-PCR is a sensitive test and a specific determination of the host species' origin. It was conducted on the CSF or saliva of the patients or tissue [15]. Brain computed tomography scan (CT scan) is usually normal in the early stage of the infection. But later evidence of cerebral edema may be detectable. A Magnetic Resonance Image (MRI) shows the area of increased T2 signal in the hippocampi, hypothalamus, and brain stem [16].

Prevention and treatment

Rabies is not a treatable but a vaccine-preventable infection. Two types of immunization did exist: Passive immunization by administering anti-rabies immunoglobulin G, shortly after high-risk bites and active immunization (vaccination) that can be used as pre-exposure prophylaxis for those at high risk of rabies and post-exposure management for those subjects who are a victim of high-risk bites, in association with passive immunization according to the official recommendation (Table 1). According to the contact severity, Post-Exposure Prophylaxis (PEP) is administered. In the case

Table 1. Rabies vaccination and immune globulin

Pre-exposure prophylaxis	Post-exposure prophylaxis
It is recommended for persons in high-risk groups, such as veterinarians, animal handlers, and certain laboratory workers	One dose of immune globulin and four doses of the rabies vaccine over 14 days (1-3-7-14 days)

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of touching or feeding animals, animals lick on the intact skin, so washing exposed skin and surfaces with no PEP is recommended. If nibbling of uncovered skin, minor scratches, or abrasions without bleeding have occurred, wound washing and immediate vaccination are necessary. Single or multiple transdermal bites or scratches, contamination of mucous membranes or broken skin with animal lick saliva, and direct contact with bats are considered severe exposure; wound washing, immediate vaccination, and administration of rabies immunoglobulin are recommended [17].

Discussion

Rabies infection causes tens of thousands of deaths every year, mainly in Asia and Africa [17]. Although rabies can be preventable after exposure, it almost always results in death once clinical manifestations develop. In this study, four cases were reported, all of whom had a salivary RT-PCR positive test, but the rabies test of any animal did not take place because it was unavailable. In the fourth case of our study, an 81-year-old woman eventually died, although vaccination and immunoglobulin received before the rabies test was positive. In the case report by Netravathi et al. [18] a 4-year-old case was presented, who received rabies immunoglobulin and vaccine (0, 3, 7, 14) and survived. However, he later developed symptoms. Perhaps she had an underlying disease such as hypertension or cardiovascular disease.

In the present study, in all of the cases at least a first dose of rabies vaccination was administered, but in Chacko's study [19] and the study by Zhu et al. [20] cases did not receive any rabies vaccine because they referred with delay and died. In our study, in three cases, vaccination was performed after the onset of clinical symptoms. Unfortunately, all of the cases died eventually; but, in a study by Hattwick [21], the case was a 6-year-old boy who was bit by a bat, and the physician initiated a 14-day course of rabies vaccine. After 20 days, severe clinical symptoms appeared, but finally, after three months, he was discharged from the hospital in good condition. Patients presented in two other studies in 2015 [18] and 2020 [22] showed that despite complete vaccination, patients developed rabies symptoms but eventually survived. These results can confirm that

vaccination can prevent death if done on time, even if severe clinical manifestations appear afterward. However, in many cases, it has been shown that timely vaccination can also prevent the onset of clinical symptoms, like a study done in 2020 with two cases received a full course of rabies vaccine without immunoglobulin and survived without any clinical manifestations [22].

In our study, the incubation period for our cases was between three days to two months. The 21-day mean incubation period for rabies in vaccinated individuals was found by Held et al. [23] in their review of 236 cases of rabies. In the present study, the duration of clinical rabies ranges from five to eight days, which is in line with a study in 2015 in which the duration of clinical rabies was ten days [20].

In our study, three cases were bitten by a dog, and one case was bitten by a fox scratch. This means that the virus has been directly transmitted to humans through animals. But there was a case in the study of Zhu [20] that the virus was transferred by humans. Therefore, the rabies virus can be transmitted indirectly to another person by an individual bitten by a rabid dog. Therefore, these people should receive a timely rabies vaccine and or anti-rabies immunoglobulin. Assessment of reservoirs of rabies in different parts of Iran shows that dogs, foxes, and jackals are the most common reservoirs of the disease in northern areas of the country [24]. Also, based on the findings by WHO, dogs are the main source of human rabies deaths, contributing up to 99% of all rabies transmissions to humans [17].

Unfortunately, most rabies survivors continue to do poorly with severe neurological disabilities, and patients are dependent on long-term care. No treatment has been yet proven effective after the onset of symptoms, and therefore, the best management is timely vaccination post-exposure.

Conclusion

As observed in this study and reported by other researchers, most cases did not receive on-time post-exposure prophylaxis. So, to decrease the mortality by rabies, increasing the knowledge and awareness of the

general population via media, brochures, and banners in the healthcare centers about the risk of rabies following animal bites particularly stray dogs, cats, etc., vaccination of pets (home dogs, cats) and requiring health care centers to follow up those victims who lost the vaccination protocol are recommended. Also, due to the highly variable incubation period, the vaccine should not be withheld for delayed presentations. Methods to increase awareness among local endemic populations to seek medical advice soon after animal exposure are needed, along with good preventive programs at the popular primary health centers to decrease the incidence of human rabies. Also, increasing awareness of the community about 24 hours active district rabies control centers is necessary. They are available on the Ministry of Health and Medical Education website.

Ethical Considerations

Compliance with ethical guidelines

Informed consent for publication was obtained from the patient or their parents. The present study was approved by the ethical committee of [Mazandaran University of Medical Sciences](#) (Code: IR.MAZUMS.REC.1401.254).

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Authors' contributions

Conceptualization and study design: Shiva Shadani, Mohammad Sadegh Rezaei; Acquisition of data: Shiva Shadani, Mohammad Reza Navaeifar, Ahmad Alikhani, Shahriar Alian, Alireza Davoudi Badabi; Drafting the manuscript: Fahimeh Ghasemi and Mahsa Kamali; Critical revision of the manuscript for important intellectual content: Mohammad Sadegh Rezaei; Supervision: Mohammad Sadegh Rezaei.

Conflicts of interest

The authors declared no conflict of interest.

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