# Complete Recovery from Clinical Rabies: Case Report

## Klinik Kuduzdan Tam Düzelme

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**ABSTRACT** A 17-year-old male had been bitten by his dog. He was given one dose of rabies vaccine after being bitten. Twenty days after vaccination, he developed complaints of itching and paresthesia at the bite area on his forearm. He was transferred to our department with the preliminary diagnosis of rabies due to his complaints of fever, abdominal pain, dysphagia and difficulty of breathing after 3-5 days. Rabies viral nucleic acid was positive by reverse transcriptase polymeraze chain reaction in the cerebrospinal fluid and saliva samples, and corneal smear was found positive with fluorescence antibody method. Patient's complaints markedly subsided after hospitalization and he was discharged on 66th day with complete recovery. In the literature, complete recovery in patients with clinical rabies is limited to a few cases. In this paper, we present the first case recovering from human clinical rabies, whose diagnosis was confirmed by direct diagnostic methods.

**Key Words:** Rabies; remission, spontaneous

**ÖZET** On yedi yaşında erkek, kendi köpeği tarafından ısırıldı. Isırıldıktan sonra bir doz kuduz aşısı yapıldı. Aşıdan 20 gün sonra ön koldaki ısırık bölgesinde kaşınma, parestezi gelişti. Üç-beş gün sonra ateş, karın ağrısı, disfaji ve solunum güçlüğü şikayetleri nedeniyle, kuduz ön tanısıyla bölümümüze nakledildi. Revers transkriptaz polimeraz zincir reaksiyonu ile beyin-omurilik sıvısı ve tükrük örneğinde kuduz viral nükleik asit pozitifti ve floresan antikor metodu ile kornea sürüntüsünde pozitif bulundu. Hastaneye yattıktan sonra hastanın şikayetleri belirgin olarak azaldı ve 66. günde tam düzelmeyle taburcu edildi. Literatürde klinik kuduzdan düzelen hastaların sayısı birkaç olguyla sınırlıdır. Bu yazıda, tanısı direkt tanısal yöntemlerle doğrulanan ve iyileşen ilk insan kuduz olgusunu sunuyoruz.

**Anahtar Kelimeler:** Kuduz; remisyon, spontan

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Rabies is a zoonotic disease producing an almost uniformly fatal encephalitis in humans and most other mammals and it is caused by Rabies virus, a member of the genus Lyssavirus, part of the large family of Rhabdoviruses.[1,2]

The patients who did not receive pre-exposure or post-exposure prophylaxis always develop clinical rabies, and the course is fatal.[1,3] Death usually occurs within 5-7 days of the onset of clinical findings unless supportive intensive care is given.[4] It has been reported that the supportive treatment in intensive care unit could not increase the survival more than 3 weeks in most cases, but prolonged the survival up to 133 days in

only one case.[5,6] However, there are six well-documented cases of recovery from rabies in the literature after the clinical presentation developed.[7]

In this paper, we present the first human case who recovered from clinical rabies after the development of clinical picture and whose diagnosis was confirmed by direct diagnostic methods.

## CASE REPORT

A 17-year-old male patient who was a shepherd had been bitten from his medial flexor antecubital area of his left forearm and right shoulder by his shepherd dog about one month ago, when he was trying to tie his dog which went furious in the last days. Upon the death of the dog 3 days later, he attended to the local health center and was given one dose of rabies vaccine (Verorab 0.5 ml, Sanofi Pasteur SA Lyon-France), 4 days after being bitten. He did not continue the vaccination calendar and developed complaints of itching, pain and paresthesia at the site of exposure in the left forearm. Because of fever, abdominal pain, dysphagia and difficulty of breathing, he was referred to the Van State Hospital and sent to our hospital with the preliminary diagnosis of rabies.

The patient was seen in the Emergency Department of our hospital and then hospitalized. He had agitation, fever, loss of appetite, crampy abdominal pain, dysphagia especially to water, breathing difficulty, hydrophobia, slight photophobia and aerophobic complaints as well as the itching and paresthesia at the exposure site. He was dehydrated since he could not drink water due to hydrophobia. His eyeballs were sunken and skin turgor tonus was diminished. When we asked him to drink a glass of water by force he sipped it with difficulty. His attempt to drink caused a choking sense with a severe discomfort in his throat as well as swallowing difficulty. This caused a short, quick inspiration, holding breath and he refused to drink the water. Despite our insistent questions, he replied us either with a sign language or with short meaningless words (dysphonia) and he was unwilling to speak with us, therefore we could cooperate with him only with the help of his family. In his history taken from his family, we learned that he was covering his eyes with his arm, saying "why is the sun shining so much?", he was feeling uneasiness from ambulance lights, sound and wind, his speech was weak and hoarse, he was refusing to drink water.

On the physical examination, his body temperature was 38.4C°, blood pressure was 110/80 mmHg, pulse:96/min, breath:24/min. His oropharynx seemed dehydrated and his tongue was dry. He had an apparent bite scar in medial flexor antecubital region of his left forearm. In laboratory examinations, white blood cell count was 17 000/mm$^3$, hemoglobin 16.7 g/dL, platelets 206 000/mm$^3$, ALT:176 IU/L, AST:106 IU/L, LDH:675 IU/L, CPK:1945 IU/L.

With these findings, he was diagnosed with rabies and transferred to a single room for the isolation for droplet and contact precautions. Anti-rabies Immunoglobulin (EQUIRAB 1000IU/5 mL, Bharat Serums and Vaccines Ltd. Ambernath) was administered at a dose of 40 IU/kg, half of it to around bite scar and the other half from gluteal region simultaneously with the Rabies vaccine (Verorab 0,5 mL) performed intramuscularly from the deltoid region.

On the first day of intravenous fluid and supportive treatment, the patient could not drink water. He was not able to swallow the water and took only a sip of water from the glass when we forced him to drink, and this was causing a hold of breath. He was not able to swallow his saliva due to dysphagia, so the saliva was accumulating in his mouth. He insisted on not to speak, and his aerophobic and photophobic complaints continued. On the second day of his hospitalization, his dehydration completely recovered and his other complaints and general status partially improved.

On the second day of the hospitalization, specimens taken from the patient were sent to the Ministry of Agriculture and Rural Affairs, Directorate of Etlik Central Veterinary Control and Research Institute-Rabies Diagnosis Laboratory. Rabies viral nucleic acid was found positive by reverse transcriptase-polymerase chain reaction (RT-PCR) in

the cerebrospinal fluid (CSF) sample, but the samples of saliva and nape of the neck biopsy were negative. Rabies antibodies were >1.5 IU/L (1:46) in the serum sample by Rapid Fluorescent Focus Inhibition Test (RFFIT). CSF sample which was found positive for rabies viral nucleic acid was negative with mouse inoculation test. However, this negativity was attributed to the increased rabies antibodies.

After 3 days, the patient could reply our questions with short meaningful answers and his aerophobic, photophobic and hydrophobic complaints regressed. He was vaccinated according to the recommended schedule. Dating from the seventh day, his complaints apparently diminished and his routine laboratory tests were normal except a slight elevation of the liver enzymes. In addition, he was able to drink a glass of water by sipping when he was forced to. Thus, samples for rabies were sent again. The rabies viral nucleic acid was found positive in saliva sample, but it was negative in CSF sample with RT-PCR method. Rabies viral antigen was positive in corneal smear sample with fluorescence antibody (FAT) method, and the antibody titer in the serum sample was >40.5 IU/mL (1:1262) by RFFIT method. When this serum sample was studied in higher dilutions, the titration was 121.5 IU/mL (1:3788).

The laboratory tests were repeated every week. Viral RNA was studied 7 times in saliva samples with RT-PCR, the titer was found positive in the second sample and gradually decreased to become negative in the seventh sample. Corneal smear samples were studied 6 times, the first sample was not proper so not studied, the next three samples were positive 3 times with one-week intervals, and the last two samples were negative. The evaluation of serum rabies antibody titers is shown in Table 1.

Directorate of Etlik Central Veterinary Control and Research Institute, Rabies Diagnostic Laboratory declared that there was a similarity between our patient's sequence analyses of RNA samples which was found positive by RT-PCR and the sequence analyses of rabies virus species which were previously isolated from Eastern Anatolian Region of our country, now present in the Virus Bank of the same laboratory.[8-10]

**TABLE 1:** Changes in serum neutralizing antibody titers.

| Date | Neutralizing Antibody | RFFIT IU/mL |
|---|---|---|
| Jul 31, 2008 | (1: 46.77) | ≥1.5 IU/mL |
| Aug 07, 2008 | (1: 1262.76) | ≥40.5 IU/mL |
| Aug 21,2008 | (1: 1262.76) | ≥40.5 IU/mL |
| Aug 28, 2008 | (1: 1262.76 ) | ≥30.8 IU/mL |
| Sep 04, 2008 | (1: 1661.76) | ≥40.5 IU/mL |
| Oct 16, 2008 | (1: 3788) | 121.5 IU/mL |
| Oct 23, 2008 | (1: 81.77) | 2.6 IU/mL |

Negativity in tests was first detected in the corneal smear samples with FAT when all complaints and general status of the patient fully improved. When his saliva was negative with RT-PCR method repeated after 14 days, he was discharged from the hospital with full recovery on the 66th day of his hospitalization.

## DISCUSSION

Rabies is a zoonotic disease worldwide with the exception of a few islands in the Continent of North Australia and Antarctica.[1,11] World Health Organization (WHO) have reported annually 55 000 deaths from human rabies accounting from dogs. Same authors claim that this figure is lower than the estimated and the real number is about 100 000.[1,12]

WHO estimates that 10-12 million people are vaccinated for post-exposure rabies prophylaxis each year worldwide.[3] Thanks to the modern vaccines beginning to be applied dating from 1987 in our country, the annual number of human rabies cases diminished dramatically and reduced to one-digit figures.[11]

Human rabies is always accepted as a fatal disease after the clinical picture develops.[3,13] However, 6 adequately documented cases of recovery from clinical rabies have been reported in the literature.[7,14-18] These cases include one case of a laboratory worker with a history of pre-exposure vaccination, 4 cases who were immunized by using

different vaccines after exposure before the beginning of the disease findings and one case without a history of immunization.[7,14-18] In only one among these cases, there was adequate neurologic improvement.[15] No rabies virus or antigen was detected in any of them and all were diagnosed serologically (Presence of too high neutralizing anti-rabies antibody titers to obtain with vaccination in either serum or CSF) along with epidemiologic and clinical features. Epidemiologic, clinical and laboratory findings of 4 of them, which had a history of post-exposure prophylaxis and adequate data, are compared with findings of our case in Table 2.

During the incubation period, no diagnostic studies are useful in the patient; recognition of an exposure to a potentially rabid animal should prompt prophylactic treatment. Laboratory diagnosis is achieved by virus isolation, histopathological examination, by identifying virus antigens by FAT and molecular methods, and by detecting antibody in serological tests.[1,11] Detection of neutralizing antibody by RFFIT which is a quite sensitive method appearing in 48 hours is possible on the 6$^{th}$ day, it is found positive in the half of the cases on the eighth day and in all of the cases on the second week.[1,11] WHO accepts the minimal protective antibody titer against rabies as 0.5 IU/L (1:5) by RFFIT method.[1,3]

**TABLE 2:** Epidemiologic, clinic and laboratory findings of the cases recovered from clinical rabies.

| Case | Madhusudana[18] | Alvarez[17] | Porras[16] | Hatwick[15] | Present case |
|---|---|---|---|---|---|
| Country | India | Mexico | Latin America | North America | Turkey |
| Age | 6 | 9 | 45 | 6 | 17 |
| Sex | F | M | F | M | M |
| Resource | Dog | Dog | Dog | Bat | Dog |
| Bite Area | Face and hands | Forehead, nose and left cheek | Multiple and deep | Left thumb | Left forearm and right shoulder |
| Rabid Animal Diagnosis | Died | Laboratoy | Clinical | Laboratoy | Died |
| Local Wound Treatment | Not done | Done | Done | Done | Done |
| Vaccine Onset and Schedule | Post-exposure 4$^{th}$ day, On day 0,3 and 7 and 14 | Post-exposure First day, On day 0,3,7,14 and additional 30 | Post-exposure 10$^{th}$ day, 14 Course additional 2 booster doses | Post-exposure 4$^{th}$ day, 14 Course | Post-exposure 4$^{th}$ day, Single dose |
| Vaccine Type | PCECV 3 doses HDCV 1 dose | VERO | SMB | DEV | VERO |
| Anti-rabies Serum or RIG | -- | -- | -- | -- | RIG |
| Initial Symptoms | 16$^{th}$ day | 17$^{th}$ day, Fever and dysphagia | 22$^{rd}$ day, Left arm paresthesia | 20$^{th}$ day, Neck pain | 20$^{th}$ day, Itching, pain and paresthesia |
| Serum Antibody Titer Peak | 90$^{th}$ day, 1:265.000 | 39$^{th}$ day, 1:34.800 | 69$^{th}$ day, 1:640.000* | 3$^{th}$ month, 1:63.000 | 76$^{th}$ day, 1: 3788 |
| CSF Antibody Titer Peak | 90$^{th}$ day, 1:124.000 | 39$^{th}$ day, 1: 78.125 | 120$^{th}$ day, 1:160.00* | 43$^{th}$ day, 1:3200 | -- |
| FAT | N | N | N | -- | P |
| PCR | -- | -- | -- | -- | P |
| Virus isolation | N | N | N | N | N |
| Outcome | Neurologic Sequelae | Neurologic Sequelae | Neurologic Sequelae | Complete Recovery | Complete Recovery |

DEV: Duck Embryo Vaccine, SMB: Suckling Mouse Brain, VERO: From Kidney Cells Extracted From an African Green Monkey, PCECV: Chick Embryo Cell Vaccine, * With Atanasiu method. RIG: Rabies Immunglobuline, N: negative, P: positive, F: Female, M: Male. FAT: Fluorescence antibody method; PCR: Polymerase chain reaction; CSF: Cerebrospinal fluid.

Neutralizing antibody titer in CSF arises 3-4 days after the serum and is valuable for rabies diagnosis.[1,11] The highest serum neutralizing antibody titers which can be obtained by vaccination are reported as 1:32 as an average, 1:600 being the highest titer, with two fold dilution method for DEV.[15] Antibody titers above this level is reported to be associated with experiencing or suffering from the disease.

Our presented case is the adequately documented fifth case in the literature with a positive vaccination history after exposure and before the clinical picture developed, the second case survived after clinical picture developed and the second case completely recovered. In our case, the diagnosis was made by the following findings:

1. Epidemiologically, the presence of a history of dog which went furious in the last days and bit the other dogs, thus it was wanted to be tied but meanwhile bit our case and died 3 days later,

2. Clinical findings of rabies,

3. Detection of very high levels of rabies antibody titers by RFFIT method, higher than the neutralizing antibody titers which can occur secondary to vaccination and which can be obtained only by experiencing the disease,

4. Presence of viral antigen positivity in corneal smear sample 3 times by FAT method,

5. Detection of rabies viral nucleic acid in CSF one time and in saliva 5 times by RT-PCR,

6. Similarity between the sequence analyses of viral RNA obtained by PCR method in our case and the sequence analyses of rabies virus species previously encountered in Eastern Anatolian Region of our country.[8-10]

There is no established, specific treatment for rabies once symptoms of encephalitis begin. Despite excellent intensive care, almost all patients succumb to the disease or its complications, within a few weeks of onset. Trials of many agents have been undertaken in clinical rabies, including some combinations with interferons, interferon-inducing agents, ribavirin, amantadine, cytosine arabinoside, midazolam and ketamin, without beneficial effects.[12,13] Therefore, prophylactic procedures remain essential for pets and humans.[1,3]

In conclusion, complete recovery in patients with clinical rabies is limited to a few cases in the literature. In all of the cases except one, there is a history of pre-exposure or post-exposure immunization before clinical rabies developed. It must be considered that one dose of purified vero cell rabies vaccine Verorab has been administered to our case after exposure, and even though it was applied once, it was able to provide adequate immunization in the period of onset of clinical picture and occasioned survival of our case. However, a lot of factors such as immunological differences or the virulence of the virus species can be effective in recovery of our case.

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