Failure of Rabies Postexposure Prophylaxis In Patients Presenting with Unusual Manifestations

Prapimporn Shantavasinkul,1 Terapong Tantawichien,1,4 Supaporn Wacharaplanuadee,2 Anuruck Jeamanukoolkit,3 Piyada Udombhaisakul,1 Pairoj Chatranchukchai,1 Patarapha Wongsaorj,1 Pakamatz Khawplod,1 Henry Wilde,2,3 and Thiravat Hemachudha4

1Queen Saovabha Memorial Institute, The Thai Red Cross Society (World Health Organization Collaborating Center for Research on Rabies Pathogenesis and Prevention), Bangkok, Thailand. 2World Health Organization Collaborating Center for Research and Training in Viral Zoonoses. 3Division of Research Affairs, Department of Medicine, Chulalongkorn University, and 4Cardiovascular Unit, Department of Medicine, Police General Hospital, Bangkok, Thailand

(See the article by Shantavasinkul et al, on pages 56–60.)

We report an atypical case of paralytic rabies presenting with trismus followed by limb weakness, areflexia, ophthalmoplegia, and bilateral ptosis. Atypical presentations and history of rabies postexposure prophylaxis led to delayed diagnosis. Nucleocapsid and glycoprotein genes of rabies viruses from the patient’s and biting dog’s brains were of identical sequences.

Almost all rabies-related deaths, despite administration of postexposure prophylaxis (PEP), are related to deviations from World Health Organization (WHO) guidelines [1]. Nevertheless, true failures without recognized defects in management have been reported [2, 3]. We recently encountered another treatment failure case with atypical tetanus-like presentation.

Case report. A 33-year-old Thai man presented with a 2-day history of high-grade fever, sore throat, headache, and watery diarrhea. At the first hospital encounter, he had rigidity of the masseter muscles (lockjaw) and slurred speech. He had difficulty eating and drinking and was noted to have excessive salivation. Several diagnoses, including tetanus, were considered. He was subsequently transferred to a tertiary care hospital.

He experienced dog bites on his hands and right knee on 8 January 2009, 25 days earlier. Wounds included a 1-cm laceration on his right thumb that penetrated deep into the nail bed. He also had 2 puncture wounds (width, 0.2 cm) on his left hand and bleeding scratch wounds on his right knee. The dog was owned but never vaccinated. It was seen biting other dogs. The patient was attacked while catching the dog for veterinary observation. The dog died 3 days later and was proven to be rabid by fluorescent antibody test of brain specimens at the Queen Saovabha Memorial Institute (Bangkok, Thailand).

He underwent prompt local wound care at a nearby public health center. Rabies PEP was rendered within 6 h using the WHO-approved Thai Red Cross intradermal (ID) rabies vaccination schedule (modified TRC-ID regimen; 2-site ID injections on days 0, 3, 7, and 28). The vaccine used was purified chick embryo cell vaccine (Chiron Behring; batch 1630; potency, 8.94 IU/dose; expiration date, June 2012). The entire calculated dose of human rabies immunoglobulin (HRIG; 1300 IU per 8.7 mL; Berirab P; CSL; potency, 150–300 IU/mL; expiration date, September 2010) was infiltrated into and around all wounds at the same time as the first vaccination. In spite of much pain, this was also done to the wound at the nail bed by an experienced staff. Tetanus immunization was completed 1 year previously, so booster injection was not indicated. Purified chick embryo cell vaccination was continued on days 3 and 7 as scheduled. The patient also received another dose of HRIG (1300 IU) injected into the wounds on 12 January after positive results of the fluorescent antibody test of dog brain specimens became known. He became symptomatic 24 days after being bitten.

At admission, on 3 February, the patient was fully conscious and had a temperature of 39.6°C. He did not report any prodromal symptoms as often seen in rabies [4]. He refused to drink water and avoided exposure to light and draft. No phobic spasms were observed. Brief episodes of agitation alternating with lucid calm were noted. Trismus and hypersalivation were evident. Laboratory studies were unremarkable except for leukocytosis (white blood cell count, 12,200 cells/μL, with 85% neutrophils).

Lumbar puncture revealed a pleocytosis level of 1120 cells/mm³ (82% monocytes, 18% neutrophils), a protein level of 95 mg/dL, and a sugar level of 70 mg/dL. Examination of cerebrospinal fluid (CSF), saliva, and urine specimens and hair follicles using a previously described method [5] for the detection of rabies viral RNA yielded negative results.
The patient remained febrile and was restless, with profuse sweating during the second day. Trismus became more severe, and he was unable to open his mouth and speak. Intermittent spasms of the neck and back muscles were noted, but without rigidity of the axial musculature. He remained fully alert and oriented. Left facial weakness of the upper motor neuron type with bilateral incomplete ptosis was detected. Pupils were 5 mm, equally reactive to light. External squint of the right eye was shown on primary gaze. Limited adduction of the left eye was noted but without accompanying abducting nystagmus of the right eye on performing right lateral gaze. Convergence was impaired. Corneal reflexes and other cranial nerve functions were normal. There was no demonstrable weakness. Sensation was normal in all modalities. Deep tendon reflexes were 4+. Plantar responses were flexor, and clonus was absent.

Conditions deteriorated rapidly 3 h later. Proximal muscle weakness of both arms, of Medical Research Council muscle strength grading system grade 3/5, was demonstrated while it was preserved in the lower limbs. Deep tendon reflexes became all absent. He remained rational and arousable until developing sudden cardiac arrest (4 February). Brain tissue necropsy via a transorbital needle biopsy approach confirmed rabies by fluorescent antibody test and detected rabies viral RNA. The incubation period was 24 days, and survival time after onset was 4 days.

Discussion. The patient had rabies despite receiving appropriate treatment. PEP failure cases due to omissions and flaws in PEP have not been rare [6–10]. Nevertheless, there are reports of human rabies deaths that appeared to be due to true treatment failures [2, 3].

Our patient received proper wound care, vaccination, and HRIG within 6 h after being attacked. Although there were difficulties in infiltrating the wound at the nail bed of the right thumb, a great effort was made by experienced staff to infiltrate this wound with HRIG as recommended [11]. The only deviation from current WHO guidelines was the additional HRIG infiltration of the wounds 4 days after the first treatment. Nevertheless, he was able to mount a good antibody response above the level of 0.5 IU/mL [1], which is considered adequate for protection from rabies, because his neutralizing antibody level on day 27 was 1.39 IU/mL, as determined using the rapid fluorescent focus inhibition test. The HRIG potency was reassessed and found to be comparable with that of the manufacturer’s export certificate (280 vs 150–300 IU/mL, respectively). Although some studies suggested that RIG may suppress the antibody production when using the Zagreb (2–1–1 IM) regimen (2 injections on day 0 and 1 each on days 7 and 21) [12, 13], the TRC-ID regimen has been shown not to have any significant suppression of antibody when RIG is administered [14, 15]. The only potential hazard of repeating HRIG infiltration, especially to the wound at the nail bed, may have been trauma to the nerves at the bite site [2]. Although it was possible that the patient might have had exposures other than the one we encountered, our repeated careful detailed history and physical examination did not confirm such a possibility.

There have been reports of patients with rabies associated with dog bites who had unusual presentations in Thailand [16, 17]. Some resembled what has been reported in bat-associated cases [18, 19]. The patient described herein presented as paralytic rabies, because classic signs of rabies, such as autonomic dysfunction and phobic spasm, were not obvious [20]; he also had relatively spared consciousness (ie, lesser degree of aggression and agitation). However, initial manifestations were unusual consisting of lockjaw and abnormal eye movements. Lockjaw or trismus is a hallmark of tetanus [21]. Intermittent spasms of the back and neck muscles in this case might be misinterpreted as reflex spasms in tetanus. However, the most important sign of tetanus—sustained muscular rigidity, especially of the axial musculatures—was missing. Presence of trismus and paralysis of ≥1 cranial nerve can be a presentation of cephalic tetanus. Abnormal ocular movements, including bilateral trochlear nerve palsy (ophthalmoplegic tetanus) and downbeat nystagmus, have been reported [22]. Nonetheless, oculomotor abnormalities and facial paresis in this case appear to be manifestations of brainstem dysfunction and were unlikely due to tetanus. Our previous neuroimaging studies involving patients with rabies and rabid dogs showed the brainstem as a predilectively involved site [23, 24]. Subsequent development of weakness of limb muscles, starting at both arms where bites were incurred, followed by leg weakness accompanied by loss of deep tendon reflexes excluded tetanus and was the pattern of progression in paralytic rabies. Ascending or descending weakness can be found in paralytic rabies [25].

Miller Fisher syndrome (MFS) and Bickerstaff brainstem encephalitis (BBE), both of which are considered variants of Guillain-Barre syndrome, might complicate the diagnosis in this case [26, 27]. Ophthalmoparesis, as described in MFS and BBE, was also found in our case. Weakness of the extremities and areflexia can be found in MFS and BBE [28]. Although profound worsening of consciousness can differentiate rabies from MFS and BBE, this patient died suddenly before any clouding of sensorium developed. This might have been due to autonomic dysfunction (cardiac arrhythmia) [16]. Fever after clinical onset plus excessive salivation favored the diagnosis of paralytic rabies [20]. The myoedema sign, previously reported in paralytic rabies [29], was not present, but this was examined before weakness developed. Anti-ganglioside antibodies, as found in Guillain-Barré syndrome, MFS, and BBE, are not present in patients with paralytic rabies [25].

Marked CSF pleocytosis was also unusual [16]. It was not known whether the repeated dose of HRIG might elicit this exaggerated response. Antemortem diagnosis using molecular methods, although sensitive, is not conclusive if the results are negative [5, 30]. Viral shedding is intermittent, and it is essential to repeat the test on as many samples of CSF, saliva, urine, and hair follicles as possible. To date, a total of 50 patients with
rabies were tested at our institutions for rabies viral RNA in CSF, saliva, urine, and hair follicles; 3 had tested negative. All 3, including this patient, were cases of paralytic rabies.

This case raised the possibility of an unusual strain of rabies or other lyssavirus as cause of the disease. It has been shown that Thai bats also harbored unidentified lyssavirus(es) on the basis of the presence of cross-neutralizing antibodies against Arawan, Khujand, and Irkut [31]. Spillage of bat viruses might occur to terrestrial animals. Molecular epidemiology surveys of rabies virus from infected animals and humans in Bangkok and from the whole country did not show evidence of other than dog strains [32, 33].

Nucleocapsid (GenBank accession numbers GQ303555 and GQ303556) and glycoprotein genes (GenBank accession numbers GQ303557 and GQ303558) of rabies viruses from the patient’s and biting dog’s brains were of identical sequences.

Nucleocapsid (GenBank accession numbers GQ303555 and GQ303556) and glycoprotein genes (GenBank accession numbers GQ303557 and GQ303558) of rabies viruses from the patient’s and biting dog’s brains were of identical sequences.

Conclusions. In canine rabies–endemic countries, physicians have to be aware of atypical presentations of human rabies. Negative results of postmortem tests using molecular method must be interpreted with caution due to the intermittency of viral shedding. Although rabies PEP is virtually always effective if properly administered, it is not a complete guarantee of survival [2, 3].

Acknowledgments

We thank Dr Veera Tepsunamethon for fluorescent antibody testing and Thanphet Tantwickeen and the nursing staff at Queen Saovabha Memorial Institute for their generous support.

Financial support. The Thai Red Cross Society and the Thailand Research Fund (DBG5180026).

Potential conflicts of interest. H.W. had accepted funding for travel as speaker to scientific conferences from Sanofi Pasteur and the Swiss Serum and Vaccine Institute. All other authors: no conflicts.

References