

# Rabies, the cause of fatal encephalitis

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## Abstract

To describe the clinical progression and medical protocols applied in a 41 year old man who was bitten by a bat three months before. The patient did not ask for medical care until acute tremor and pain in the right thoracic limb and hydrophobia started. For a history of a wild animal bite associated with a unique clinical condition, we suspected of rabies encephalitis, confirming the diagnostic by pathology after his death. This case occurred in Guadalajara, Jalisco, México, in April, 2022. The last case of human rabies reported in Jalisco secondary to bat bite was almost 30 years ago. As an uncommon disease, medical personnel and facilities should be prepared to attend this sort of cases after clinical suspicion. For the present case, the medical history was the key for diagnosis. Rabies is a disease caused by the neurotropic virus belonging to the Rhabdoviridae family whose prognosis is bleak, with mortality close to 100% and therapeutic options limited. This case emphasizes the high mortality of rabies virus infection and the importance of increasing awareness and education to the public in general, with regard to applying the vaccine as post-exposure prophylaxis.

**Keywords:** rabies; infectious encephalitis; rabies encephalitis; bat

## Resumen

Describir la evolución clínica y los protocolos médicos aplicados en un hombre de 41 años que fue mordido por un murciélago tres meses antes. El paciente no solicitó manejo médico hasta que inició temblor agudo y dolor en miembro torácico derecho e hidrofobia. Por antecedente de mordedura de animal salvaje asociado a cuadro clínico único, se sospechó de encefalitis rábica, confirmándose el diagnóstico por patología tras su muerte. Este caso clínico se presentó en la ciudad de Guadalajara, Jalisco, durante el mes de abril de 2022. El último caso de rabia humana reportado en Jalisco, secundario a mordedura de murciélago, fue hace casi 30 años. Al ser una enfermedad inusual, el personal y las instalaciones médicas deben estar preparados para atender este tipo de casos luego de la sospecha clínica. Para el presente caso, la historia clínica fue clave para el diagnóstico. La rabia es una enfermedad causada por el virus neurotrópico perteneciente a la familia Rhabdoviridae, cuyo pronóstico es sombrío, con una mortalidad cercana al 100% y opciones terapéuticas limitadas. Este caso enfatiza la alta mortalidad de la infección por el virus de la rabia y la importancia de aumentar la conciencia y educación del público en general, con respecto a la aplicación de la vacuna como profilaxis post-exposición.

**Palabras clave:** rabia; encefalitis infecciosa; encefalitis rábica; murciélago

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Rabies is one of the oldest and most feared diseases among humans, it was described in approximately 4000 BC, and denoted in the sanskrit language in which "rabhas" means "assault", and causes fatal encephalomyelitis. This virus belongs to the *Lyssavirus* type of the family *Rhabdoviridae*, and is recognized as the most lethal infectious disease in humans. It can be transmitted through cuts, bites, and contact with mucous membranes, aerosol sprays, and organ transplants, as well as through tissue infections.<sup>1</sup>

In Latin America, more than 80% of all human rabies cases are transmitted by dogs. For this reason, the World Health Organization (WHO) has created global vaccine campaigns against rabies in dogs, as well as prophylactic treatment for persons exposed to the virus. In Mexico, during the 1990s, there was a notable decrease in human rabies cases transmitted by dogs, thanks to the National Canine and Feline Anti-Rabies Vaccination Week.<sup>2</sup> It was the first country in the world free of human rabies transmitted by dogs, with the last case reported in 2006. However, there are still reported cases of transmission through contact with other animals such as farm animals, especially cattle and wild animals including bats, with the latter case reported in our country in 2016, and in Jalisco in 2009.<sup>3</sup>

The incubation period in humans varies considerably, although the majority of patients develop symptoms within 20 to 90 days after exposure.<sup>4</sup> Patients generally present weakness in the bitten extremities which advances into a furious form of rabies with fluctuations of consciousness, hydrophobia, or aerophobia, and signs of autonomic dysfunction, or a paralytic form of motor affection with weakness from the bottom up, which advance from a coma to death.<sup>5</sup>

The present manuscript aims to report a case of rabies in a previously healthy young man and discuss the vital role of an accurate and timely diagnosis in the control of rabies.

### Clinical case

A 41-year-old man, born and raised in Guadalajara, Jalisco, Mexico, previously healthy, immunocompetent, with no medical record of drug abuse and no recently applied vaccines, with zoonosis by domestic fauna (four cats and four dogs) unvaccinated. He began his clinical condition on April 04 2022 that was characterized by resting tremors in the right hand accompanied by localized pain in the homolateral limb, with partial response to analgesics. The aforesaid pain raise and ascended in a progressive manner in the following 72 hours, with extension at the ipsilateral shoulder and in the cervical region, latter adding paresthesia and reduced mobility

in the limb as well as edema, reason why they attend to his second level care hospital unit where he was admitted to start the diagnostic approach. During his aforementioned stay he was treated symptomatically with parenteral analgesics, however, given the lack of improvement and the presence of intense pain, a brachial plexus blockade was decided, without a response followed by discharge. In the following 24 hours after hospital discharge, the patient experienced deterioration in his general condition, exhibiting fever and a headache, with changes in behavior that initially began with agitation, inattention, and irritability. He was therefore taken once again to a regional hospital where he was hospitalized once more and his physicians on charge decided to begin antibiotic therapy management following suspicion of a bacterial neuroinfection which was unresponsive to treatment. He was discharged against medical advice by his family members who wanted to have a neuroimaging study performed outside of the hospital. The magnetic resonance imaging (MRI) brain scan could not be performed as patient's increased agitation and irritability was registered. On April 10 2022, he began to experience sialorrhea, an aversion to water, and muscle spasms predominately in the right arm, progressing with neurological deterioration to lethargy. On April 13 2022, he was transferred by family members to our hospital center, where emergency physicians detected upon his admission a clear alteration of his state of alertness that lead to advanced management of the airway. An evaluation was subsequently requested by neurology department.

Upon our initial evaluation, the patient was under sedation, highlighting on examination sustained fever, conjunctival hyperemia, excessive drooling, isocoria 2 mm, with preserved brain stem reflexes, generalized hyperreflexia, indifferent bilateral plantar reflex, and an absence of signs of meningeal irritation. A diagnostic approach began with a cranial CT scan that yielded non-specific findings (figure 1) and a lumbar puncture to obtain information about the cerebrospinal fluid (CSF) that was clear appearance (rock water), presented pleocytosis due to polymorphonuclear leukocytes, mild hyperproteinorrachia, and a normal CSF/plasma glucose ratio (table I). It was therefore decided his hospital admission with a diagnostic for probable viral encephalitis, beginning empirical antimicrobial and antiviral therapy.

In consideration of the evolution that was present, the members of the family were directly questioned regarding risk of contact with fauna, who remember a previous bat bite from three months prior to the onset patient condition, during a family trip in the state, after which he did not seek medical attention, and as such, he did not receive prophylaxis. Because of the afore-



CT (computed tomography) scans show absence of brain sulcus markings with poor differentiation of white and gray matter from diffuse bilateral cerebral hemispheric edema and diffuse hypodense subcortical regions in the occipital lobes, predominantly on the left, without mass effect or vascular territory (Imagenology Department, Hospital de Especialidades CMNO, Guadalajara, Jalisco; April, 2022).

**FIGURE 1. CRANIAL CT SCAN (AXIAL SECTION)**

**Table I  
LABORATORY STUDIES**

LCR: Leukocytes 400 xmm<sup>3</sup>, Polymorphonuclears 95%, Mononuclears 5%, Glucose 81 mg/dl, Proteins 56 mg/dl, appearance of rock water

HIV, VHC, VHB serologies reported negative

Hb 20 gr/L, Hto 57.7%, Leu 20.60x10<sup>3</sup>/uL, Neu 17.62x10<sup>3</sup>/uL, Pla<sup>q</sup> 606 000 x10<sup>3</sup>/uL, Glucose 130 mg/dL, Urea 113.92 mg/dL, Cr 103.1 mg/dL, total bilirubin 1.98 mg/dL, direct bilirubin 0.42 mg/dL, indirect bilirubin 1.56 mg/dL, ALT 171 U/L, AST 97 U/L, P 1.5 mg/dL, Ca 12.6 mg/dL, K 3.7 mEq/L, Na 145 mEq/L, Mg 1.2 mg/dL, DHL 192 U/L, Procalcitonin 0.09 ng/mL, CPK 71 mcg/L.

Clinical Laboratory, Hospital de Especialidades CMNO, Guadalajara, Jalisco; April, 2022.

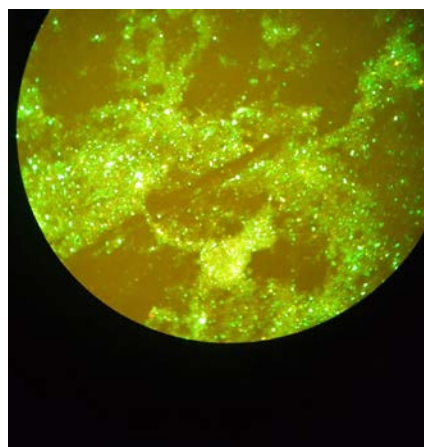
mentioned epidemiological significance, in the context of a patient diagnosed with infectious encephalitis, with signs characteristic like hydrophobia, weakness and intense pain in the affected limb, with a relatively traditional chronological evolution for the incubation, prodrome and acute neurological period, we decided to classify it as a probable case of rabies encephalitis. It was managed following the guidelines of the Milwaukee protocol, including a drug-induced coma with Midazolam and Ketamine, along with the administration of 20 units per kilogram of Gamma-Globulins and a Verocell rabies vaccine. Since his admission into the service,

the patient presented dysautonomias manifested by variability in blood pressure readings and heart rate, but after 72 hours with sustained arterial hypertension and bradycardia.

Regarding to the diagnostic approach, ophthalmology service was requested in order to carry out a corneal impression test of both eyes and to surgery service through a scalp biopsy, in addition, a saliva and CSF sample were taken. All the samples were processed in the laboratory of the The Public Health State Laboratory of Jalisco. The polymerase chain reaction (PCR) assays for determination of viral loads were reported negative. Unfortunately, in spite of the interventions of the multidisciplinary team of healthcare professionals, the patient progressed towards multiple organ failure with fatal autonomic dysfunction, and died on the fourth day of hospitalization. The family members authorized an autopsy that was carried out by the Public Health State Laboratory, where was performed a histopathologic study of the brain which utilized the direct immunofluorescence technique and the conjugate reagent FITC Anti-Rabies Monoclonal Globulin which confirmed the presence of the rabies virus (RABV) in tissue as an infectious agent (figure 2).

## Discussion

RABV causes an acute neurological infection that is deadly to humans and other mammals; it is transmitted through the saliva of infected animals,<sup>6</sup> even though it can be transmitted through contact with other fluids and tissues such as urine, sweat, or nervous tissue.<sup>7</sup>



Direct immunofluorescence technique and the conjugate reagent FITC Anti-Rabies Monoclonal Globulin in patient's brain sample (Laboratorio Estatal de Salud Pública, Guadalajara, Jalisco; April, 2022)

**FIGURE 2. DIRECT IMMUNOFLUORESCENCE ASSAY**

Although dogs are the vectors that act in the primary transmission to humans, in those countries that have a suitable vaccination schedule for domesticated animals, such as Mexico, bats are the principal vectors of transmission to humans.<sup>8</sup>

Upon inoculation, virions attached themselves to nicotinic acetylcholine receptors in local muscle tissue in order to become enlarged later on, before a retrograde transport through the peripheral nerves to the dorsal root ganglion, and ultimately, to the brain and salivary glands.<sup>9</sup> The incubation period tends to be long, on average from 1 to 3 months, as in the current case,<sup>8</sup> and may even be up to years after the incident,<sup>10</sup> which on many occasions difficult the exposure identification, in the case of our patient, spite of prior attention by multiple doctors, the history of the bat bite was recalled by the family member until she was actively questioned regarding the antecedent, since it was considered a trivial event by the patient.

Rabies in humans manifests as acute rapidly progressive encephalitis, by two different types, approximately two-thirds of infected patients present rabies encephalitis in which fluctuations of consciousness, state of alertness, hydrophobia, inspiratory spasms, and prominent autonomic dysfunction are observed, which was the form shown by our patient; and the remaining one-third presented a paralytic form (Guillain-Barré-like) that progresses into a coma, myoedema, and sphincter dysfunction. One-third of all patients have a prodromal phase that is consistent with that shown by our patient, with non-specific neuropathic pain on the site of the bite.<sup>11</sup> We believe that conducting a thorough anamnesis about the evolution of the clinical condition and symptoms that he presented, as well as the detailed initial examination to identify characteristic signs and findings distinctive of other encephalitis, such as the presence of hydrophobia, muscle spasms, excessive drooling, and dysautonomias, allowed us to integrate a strong clinical suspicion, in spite of the low prevalence of this disease; with the last case documented in our state 13 years ago.<sup>3</sup> Our patient, from the onset of his condition, exhibited trembling in the affected limb, which is observed more frequently in rabies transmitted by bats, like precisely this case, and it is consequently linked to the interaction of the structures and the pathways that include the peripheral nerves, brainstem, basal ganglia, cerebellum and white and grey matter of cerebral hemispheres.<sup>12</sup>

The procurement of cytochemical cerebrospinal fluid confirmed the presence of infectious encephalitis, and focused on viral etiology due to the presence of normal glucose levels, proteins discretely elevated, and important pleocytosis, with atypical data because

it is predominantly polymorphonuclear, since in this infection the cytochemicals CSF tend to be normal, but in a small number of cases, are present changes that are associated with viral meningoencephalitis with pleocytosis that is characteristically lymphocyte.<sup>13</sup> Regarding the neuroimaging studies, unspecific findings have been found in the cranial computed tomography (CT) scan, such as diffuse or focal hypodense areas, especially in the basal ganglia, periventricular white matter, hippocampal and brainstem, pontine hemorrhages, or diffuse cerebral edema.<sup>14</sup> In the MRI T2 weighted image hyperintense lesions can be observed in the basal ganglia, thalamus and pons, with normal magnetic angioresonance,<sup>15</sup> in this case, we could identify cerebral hemispheric edema and hypodense areas in the occipital regions, with no established arterial or venous territory, unfortunately, we could not obtain a MRI to confirm the supported findings in the CT.

To establish definitive diagnosis, there are various options that allow for the detection of the virus, they include a reverse transcription polymerase chain reaction (RT-PCR) in saliva, blood and CSF, specific CSF antibody determinations, as well as a biopsy using an immunohistochemical analysis, and RT-PCR of hair follicles and encephalon.<sup>8</sup> In our case, in accordance with the availability of diagnostic resources provided by the *Instituto de Diagnóstico y Referencia Epidemiológicos*, and by state laboratories, the conclusions of rabies encephalitis were reached through a histopathology report of an autopsy.

Notwithstanding the fight against rabies being centuries old, throughout which numerous methods have been implemented to combat it, it continues to be a cause of great concern for health personnel. The WHO, the World Organization for Animal Health (OAH), the Food and Agricultural Organization of the United Nations (FAO), and the Global Alliance for Rabies Control (GARC), have established a global multisectoral framework that is "united against rabies", in order to provide a common strategy and to achieve "zero human deaths from dog-mediated rabies by 2030".<sup>16</sup>

Until now, no standardized medical treatment has existed, in our patient, from the moment of the suspected infection, management was established according to the guidelines of the Milwaukee protocol,<sup>17</sup> which it was possible to save an infected patient for the first time, and consists of inducing a coma and treat with antiviral medications, in order to reach maturation of the primary immune response of the patient. In addition, 20 units per kilogram of Gamma-Globulins and a single dose of Vero-cell rabies vaccine were administered. Even though mortality is very close to 100%, a little more than 20 survivors have been registered thus far, the overwhelming

majority of whom have severe neurological sequelae.<sup>4,18</sup> However, paradoxically, rabies also has the distinction of being 100% preventable with the establishment of a post-exposure prophylaxis in a timely and appropriate manner.

As mentioned above, rabies transmitted by dogs and cats has been practically eradicated from our country. The low frequency of cases means that clinicians have extremely low or null diagnostic suspicion, especially in late stages of the disease, as occurred in the case presented. Regarding the above, it is expected that the health personnel are not completely familiar with the protocols to follow. Among the details that need to be known is the opportunity for rapid diagnosis in a living patient through corneal imprints. It is important to know that they must be taken before the application of any treatment scheme with immunoglobulins or Vero cells. Likewise, it is important that health personnel are ready to take samples of the scalp and saliva. The preparation of the samples must include their proper identification and packaging.

Many other things about the case can be shared and useful. As a first point, the medical history, whether direct or indirect, is essential to reach the diagnosis. It is also important, in all cases of encephalitis, to maintain droplet and contact isolation to avoid infection through secretions and to use personal protective equipment, especially in intubated patients due to the infectious potential of airborne particles.<sup>19</sup> Details like this are unknown to most since the description is not available in most national and international guides since most talk about the transmission of the disease from animals to humans, but little is written about the transmission from human to human. The above can be put on the table and discussed since although there is no evidence to confirm it, there is also no evidence to rule it out. Given this situation, we believe that at the time of diagnosis, the local and national authorities should be informed immediately to open the case (outbreak) and carry out a study of the contacts. Each contact must be questioned efficiently and determine if they require post-exposure prophylaxis, which in this case was managed with human rabies immunoglobulin 20 IU per kilogram of weight, a single intramuscular dose and Vero cell regimen on days 0, 3, 7 and 14. Also intramuscularly in all contacts. The recommendation is to implement the prophylaxis schedule within seven days of exposure.

Finally, the communication role between institutions has played to achieve better results is of great importance, since in the present case, the *Instituto Mexicano del Seguro Social* (IMSS), the *Secretaría de Salud Jalisco* and the *Centro Nacional de Programas Preventivos y Control de Enfermedades* (Cenaprece) worked together,

achieving favorable results. Beyond the clinical setting, an intervention was carried out within 72 hours of case notification, with an anti-rabies vaccination campaign for dogs and cats in the area where the bat bite occurred, as well as the collection of bat specimens for their study.

Despite the low possibility of another similar case, it is important that the authorities in charge of epidemiological surveillance review the information on the risk of contagion in the general population and, above all, maintain continuous training of health personnel to be available and act promptly and efficiently in case of a new case.

## Conclusion

Rabies encephalitis has the highest death rate among all the different forms of viral encephalitis and a timely diagnosis requires a higher index of suspicion criteria, the foregoing owing to supplementary diagnostic tests that are not always available and/or initial lab studies that can result negative. Therefore, it is imperative for the clinic, without excluding the most common neuroinfectious etiologies, to pay close attention to, or to probe in a direct and thorough manner, regarding the details and or specific nuances that are present in the evolution of the patient, thereby exploiting to the fullest and in its entirety, the history of the patient, which continues to be the first and foremost tool in clinical practice.

This case is a clear example of how underestimating a disease, with a low index of suspicion and an unusual clinical case of neuroinfection, can delay a diagnosis of rabies, and more important, emphasize the importance of increasing public awareness of the importance of establishing a post-exposure prophylaxis for those contacts who are at risk that in turn can completely change the patient scenario.

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