https://doi.org/10.21708/avb.2022.16.2.10310

Rabies in a previously vaccinated horse: case report

Raiva em equino previamente vacinado: relato de caso

Clarisse Simões Coelho[1,2*], Ticiane d'El Rei Passos Sodré[3], Moises Dias Freitas[2], Ludmila Rodrigues Moroz[4], Talyta Lins Nunes[2], Tiago da Cunha Peixoto[2], Paula Velozo Leal[2]

ABSTRACT: Rabies is an acute, progressive, and fatal encephalomyelitis caused by a Lyssavirus. Horses affected by the disease may be a source of infection for humans. A rapid diagnosis is crucial to initiate a prompt and adequate infection control and public health measures. This manuscript reports the case of a 4-year-old gelding, 370 kg, healthy and routinely used for veterinary teaching purposes that developed rabies although vaccinated against it. Clinical signs included lameness, ataxia, muscle tremors, decubitus and pedalling, progressive paralysis, profuse salivation, teeth grinding, and whinnying. After 4 days, the animal was euthanised and definitive diagnosis was achieved through an animal inoculation test which was positive. Complementary findings included encephalomyelitis with perivascular cuffs and identification of Negri bodies in various areas of the brain.

KEYWORDS: equine; Negri body; neurology; zoonosis.

RESUMO: A raiva é uma encefalomielite aguda, progressiva e fatal causada por um Lyssavirus. Cavalos acometidos pela doença podem ser uma fonte de infecção para homens. O rápido diagnóstico é crucial para que iniciem medidas de controle de infecção e de saúde pública adequadas. Esse manuscrito descreve o caso clínico de um equino de 4 anos, macho castrado, 370 kg, hígido, usado nas práticas didáticas da escola de veterinária que desenvolveu quadro clínico de raiva, apesar de ser vacinado contra a referida doença. Os sinais clínicos incluíram claudicação, ataxia, tremores musculares, decúbito e movimentos de pedalagem, paralisia progressiva, salivação profusa, bruxismo e relinchos. Após 4 dias, o animal foi eutanasiado e o diagnóstico definitivo foi feito através de prova biológica positivada. Os achados complementares incluíram os achados histopatológicos nos quais destacam-se encefamolielite com manguitos perivasculares e identificação de Corpúsculos de Negri em várias áreas do cérebro.

PALAVRAS-CHAVE: equinos; corpúsculos de Negri; neurologia; zoonose.

INTRODUCTION

Rabies is a zoonotic neurological disease of mammals (ACHKAR et al., 2010) and it is almost invariably fatal once the clinical signs develop (BASSUINO et al., 2016). It is caused by neurotropic viruses (RABV), genus *Lyssavirus*, family Rhabdoviridae (MANNING et al., 2008; ACHKAR et al., 2010; TOLOUEI; MOBARAK; MOSTOFI, 2017). Exposure can occur through the bite of an infected animal or less commonly by contact with infectious saliva or neurological tissues through mucous membranes or breaks in the skin (MANNING et al., 2008; ACHKAR et al., 2010). During the eclipse phase (incubation period), the virus replicates in non-nervous tissues such as muscles. At this point, the virus is not detected by the immune system and does not stimulate an immune response. However, it can be neutralized by antibodies if present. After days or months, virus migrates via nerves to the brain where it initiates a rapidly progressive, almost always fatal encephalitis (MANNNING et al., 2008; BASSUINO et al., 2016).

According to OIE (2008), rabies virus is found worldwide. Prevalence rates are high in some parts of the developing world (LACKAY et al., 2008; WILDE; HEMACHUDBA; JACKSON, 2008), and 90% of human rabies cases occur after exposure to rabid dogs. Transmission from herbivores is low because they usually develop paralytic characteristics and not the furious form as occurs in dogs/cats (ACHKAR et al., 2010). Furthermore, they usually die within a short period

[1]Faculdade de Medicina Veterinária, Universidade Lusófona de Humanidades e Tecnologias (ULHT)/ Escola Superior de Saúde, Proteção e Bem Estar Animal, Curso de Enfermagem - IPLUSO. Campo Grande 376, 1749-024 Lisboa, Portugal. Telephone: +351 935125059.
[2]Departamento de Anatomia, Patologia e Clínicas Veterinárias, Escola de Medicina Veterinária e Zootecnia. Universidade Federal da Bahia (UFBA). Avenida Adhemar de Barros 500, CEP: 40170-110, Salvador – BA, Brazil.
[3]Pós-Graduanda. Programa de Pós-Graduação em Ciência Animal nos Trópicos, UFBA, Salvador – BA, Brazil.
[4]Laboratório de Análises Clínicas, Hospital de Medicina Veterinária Renato R. de Medeiros Neto (LAC-HOSPMEV), UFBA, Salvador – BA, Brazil.
*Corresponding author: clarissecoelho@yahoo.com.br
Received: 04/03/2021. Accepted: 22/04/2021

of time after clinical signs are seen. In South America, rabies in herbivores usually is transmitted by hematophagous bat *Desmodus rotundus* (BASSUINO et al., 2016). The disease is endemic in Brazil, where it is a mandatory reportable disease, and it is indicated as one of the major diseases of the nervous system of horses (DOGNANI et al., 2016).

In equids the incubation period is reported to be from 25 days to more than 5 months in bat-transmitted rabies and is dependent on; wound severity, wound distance from the brain, amount, and strain of the virus (TOLOUEI; MOBARAK; MOSTOFI, 2017). Clinical signs are not characteristic and include (OIE, 2008); restlessness, anorexia, dilation of the pupils, hyperreactivity, behavior and temperament changes, followed by a progressive unexplained paralysis, lasting for 2 to 5 days. Diagnosis relies on laboratory testing of refrigerated specimens that should be sent to the laboratory by the fastest means available (BASSUINO et al., 2016). The most widely used test is the direct fluorescent antibody test (dFAT), which is recommended by World Health Organization (WHO) (OIE, 2008). In cases of inconclusive results (dFAT, for example), further confirmatory tests (molecular tests, cell culture or mouse inoculation tests - MIT) on the same sample are recommended. MIT can be easily and practicably applied in situations where skills and facilities for other tests (e.g., cell culture) are not available (OIE, 2008; ACHKAR et al., 2010). Previous research has shown that dFAT, MIT and Negri bodies were respectively found positive in 98%, 95% and 53% in animals with rabies (ZIMMER et al., 1990).

As it has a considerable public health significance (WILDE; HEMACHUDBA; JACKSON, 2008), rabies vaccination is recommended to be administered to all equids annually; however, it is not obligatory in Brazil. Besides systematic vaccination, control of herbivore rabies should include bat control, health education and vaccination of dogs and cats (ACHKAR et al., 2010). The main purpose of this case report is to describe a naturally occurring case of rabies in a previously vaccinated horse.

CASE REPORT

This case reports a 370 kg, 4-year-old mixed breeding gelding, routinely used for equine-related teaching classes at the Veterinary School of Universidade Federal da Bahia (UFBA), considered healthy until sudden manifestations of neurological clinical signs in July 2019. This particular horse was housed with a mare in the same paddock and nearby other animals such as bovines and ovines. In the paddock, they had free access to grass and hay (*Cynodon* sp.) and water, and their diet also included commercial concentrate (0.5 kg/100 kg body weight - ProEqui, Guabi, Brazil) with 13% crude protein and 3,043 kcal/kg energy level, once per day, in the morning (7AM). The animal was examined regularly, including physical and laboratorial exams, to evaluate its health. Health management included deworming based on parasitological tests, with the last administration of ivermectin in April 2019 (200 mcg/kg, PO, Ivermic, Microsules Laboratory, Uruguay). Immunization schedule for both horses, as well as for the all equines of the school facilities, included rabies (2 mL, IM, once a year, RaivaCel Multi - inactivated Pasteur strain virus produced in cell culture, MSD Saúde Animal, Brazil) and equine encephalomyelitis, tetanus, and influenza (1 mL, IM, once a year, TriEqui, CEVA, Brazil). The last booster against rabies occurred in March 2019 and was performed by the veterinarians of the university using the same brand as previously described. The vaccines were stored between 2°C and 8°C, following manufacturer's recommendations, until administration.

In July 2019, the animal was found in left lateral recumbency near the fence in the paddock, unable to stand on his own (Figure 1). A preliminary physical examination was performed with a heart rate (HR) of 72 beats/minute, cutaneous turgor of <1 second, congested eyes with normal oral mucous membranous and he was responsive with some uncommon head shaking. No wounds were observed. Because of the rainy day and a very muddy pasture the early diagnosis was trauma. Flunixin meglumine (1.1 mg/kg) was administered through an intravenous injection and after 15 minutes he could stand up with some help. Then, he was taken to the veterinary hospital. While walking he exhibited signs of lameness in the right hindlimb with muscle tremors. Because of some abdominal discomfort and hindgut hypermotility he was

Figure 1. Gelding found in left lateral recumbency at a muddy paddock a rainy day.

treated with scopolamine (0.3 mg/kg, IV). However, he fell again followed by pedaling limb movements. Although the first clinical suspicion was still some type of trauma, differential diagnosis included equine encephalomyelitis and rabies. Considering this, all the veterinarian team was equipped with personal protective equipment (PPE) and continued throughout the treatment. Treatment was continued with intravenous administration of DMSO (1 g/kg, 10% solution, q24h) and fluid therapy (lactated Ringer's solution, 2.5 mL/kg/h). After a couple of hours, he could stand up again with help; however, clinical signs worsened. Although conscious, he had ataxia, gait abnormalities, proprioceptive deficits, forward fetlock knuckling of both hindlimbs, leading to a dropped hip. He was taken to a stall with rubber flooring where the treatment was continued. Again, he fell showing intense agitation behavior (whinnying, pedaling movements of the hindlimbs, "pinched" facial expression, teeth grinding). New medications were administered trying to control these new clinical signs; acepromazine (0.05 mg/kg, IV, q8h), phenylbutazone (4.4 mg/kg, IV, q12h) and dexamethasone (0.1 mg/kg, IV, q24h), while continuing with fluid therapy previously initiated. The agitation worsened and detomidine (15 mcg/kg, IV) was used for sedation and repeated as needed. During the first night, all physical parameters remained constant with HR of 60 beats/min, respiratory rate (RR) of 16 mov/min, rectal body temperature (BT) of 37°C with normal intestinal motility but no defecation.

After 24 hours (day 1), his condition worsened with constant excitation, decrease of tail and anal tone, hypoesthesia of the hindlimbs and intense pedaling movements of forelimbs, lateral recumbency, "pinched" facial expression and whinnying. Although sometimes conscious, the animal alternated periods of dullness and stupor. He was not able to swallow, even though thirsty. Analysis of cisternal cerebrospinal fluid showed no abnormalities and it was negative on indirect immunofluorescence antibody test for *Sarcocystis neurona*. Blood analysis revealed a considerable increase in serum creatine kinase level (11,150 IU/L). Lack of response to drug therapy and worsening of the condition raised the possibility of rabies, even with previous vaccination.

Between day 2 and 3, signs of disease progression were observed as hindlimb paralysis, bladder paralysis, absence of recto-anal and perineal reflexes, polypnea, bruxism and agitation. Physical parameters were HR of 43-60 beats/min, RR of 30-46 mov/min, BT of 37.5-38.1°C and intestinal hypotonia. An antibiotic regimen was initiated (ceftiofur, 2.2 mg/kg, IM, q24h) along with supportive care which included supplementation of IV nutrients, manual rectal evacuation, and bladder catheterization (to facilitate fecal and urinary decompression), turning (over the ventrum) every 8-12 hours, treatment and protection of decubital ulcers and caecum decompression.

On day 3 there was still no response to clinical therapy observed and neurological signs continued to worsen. The horse also exhibited opisthotonos, frequent and intense leg-pedaling movements of forelimbs, as well as teeth grinding, mydriasis and slow pupillary reflex, longer periods of stupor and sweating. By the end of the day, he manifested hyperesthesia, weakness, convulsions, hyperactivity with no response to sedatives.

Euthanasia was performed on day 4 to reduce animal suffering and biological risk for the veterinarian team as rabies was the principal differential at this point. At necropsy it was possible to observe multiple areas of decubitus ulcers associated with yellowish and moderate subcutaneous edema over the forelimbs, tuber-coxae, thorax, abdomen, head and neck. Other significant findings included a full bladder, engorged leptomeningeal vessels and hemorrhage of the white matter of the spinal cord (more intense at sacral lumbar and thoracic regions). No macroscopic lesions were observed on other organs. Tissue was fixed in 10% buffered formalin for histological processing and hematoxylin and eosin staining. Samples from cortex, thalamus, hippocampus, cerebellum, brainstem and spinal cord (cervical, thoracic and lumbar) were collected and sent under refrigeration to a regional reference laboratory; Laboratório Central de Saúde Pública da Bahia (Central Laboratory of Public Health of Bahia, LACEN, Salvador, Brazil), for direct fluorescent antibody test (dFAT), which tested negative in two analysis, and mouse inoculation test (MIT) that was positive (after 12 days of inoculation in new-born mice). Both tests are recommended by Brazilian legislation for rabies diagnosis.

The only histologic changes were in the central nervous system and they consisted of perivascular inflammatory infiltration formed by 12 layers of lymphocytes and plasmacytes diffusely arranged in the Virchow Robins spaces (Figure 2) from the cortex to the sacral region of the medulla. Negri bodies (eosinophilic, sharply outlined, inclusion bodies) (Figure 3) were found within cytoplasm of nerve cells, more often in Purkinje cells of the cerebellum and neurons of the pons and

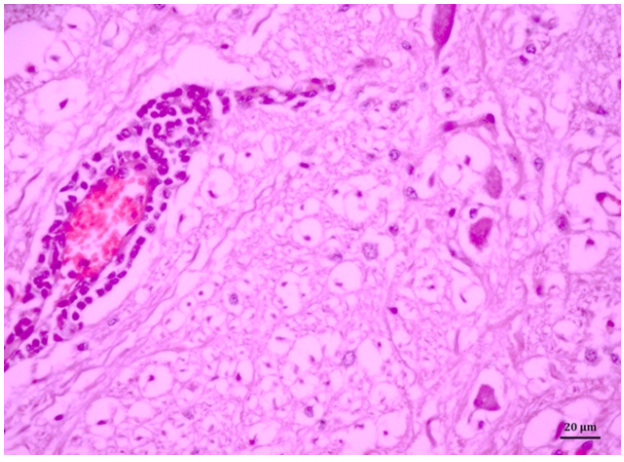

Figure 2. Spinal cord (Lumbar). Perivascular cuffs and focal gliosis in a horse. H&E. 400x

thalamus. There was intense congestion and multiple areas of hemorrhage throughout the parenchyma with moderate neuronal degeneration characterized by central chromatolysis and vacuolization.

DISCUSSION

According to Lima et al. (2005), Pedroso et al. (2010) and Bassuino et al. (2016), equine rabies is poorly studied in Brazil although considered of great importance in herbivores (DOGNANI et al., 2016). It remains clinically indistinguishable from other types of encephalitis (BASSUINO et al., 2016). Herbivores tend to exhibit paralytic signs of rabies (tail and hindlimbs paralysis, lateral recumbency, pedaling movements, bladder atony, convulsions and, eventually, changes in mental status), with 3.6 days of progression (ACHKARD et al., 2010; PEDROSO et al., 2010; TOLOUEI; MOBARAK; MOSTOFI, 2017). These reports are similar to observations made on the reported case. While the main form of transmission is through bites and contact with rabid saliva and horses act as sentinels and terminal hosts of the disease (ACHKARD et al., 2010), care was taken to avoid possible potential transmission (TOLOUEI; MOBARAK; MOSTOFI, 2017).

The initial differential was trauma due the fact that the horse was young, had no signs of bat bite wounds, and recent rainfalls caused the paddock to be wet and slippery. Furthermore, the horse had a history of continuous and current vaccination against rabies. Protective immunity against rabies is complex as antibody titers alone do not always directly correlate with absolute protection against lethal infection. In animals, some studies observed protection after a single administration of a pre-exposure dose of rabies vaccine for a minimum duration of 1-4 years (MANNING et al., 2008; HARVEY et al., 2016). However, in horses, anti-rabies titers generated by a single dose of rabies vaccine were < 0.5 IU after 8 weeks of vaccination (82% of aged horses and 50% of younger horses), making a booster necessary (MUIRHEAD et al., 2008). Considering this data, the anti-rabies vaccination protocol adopted by the veterinarian team at UFBA for all herbivores, which included the reported gelding, is a first dose at 3 months of age, with a booster 30 days after and annual revaccination. Dogs and cats with a history of vaccination are unlikely to become infected with rabies (ENG; FISHBEIN, 1990). However, in one study,14.6% of horses were poor responders to vaccination (HARVEY et al., 2016) although other reports described a 100% efficacy of an inactivated equine rabies virus vaccine (BARNETT et al., 2009). Consequently, there is a possibility of a non-response to vaccination (anergic-like response) of the gelding. A serological evaluation was not performed due to financial limitations and lack of resources in our institution to perform it. Vaccination does not equate to immunization and there is always the possibility of failure which is a matter of concern when considering rabies. This premise was strongly considered in this horse. Although not confirmed, he also showed mild signs of tetanus while vaccinated two years before rabies diagnosis (in 2017). It is important to reinforce that all other herbivores of the same herd received the same vaccine brand and protocol against rabies and only this animal had shown neurological signs.

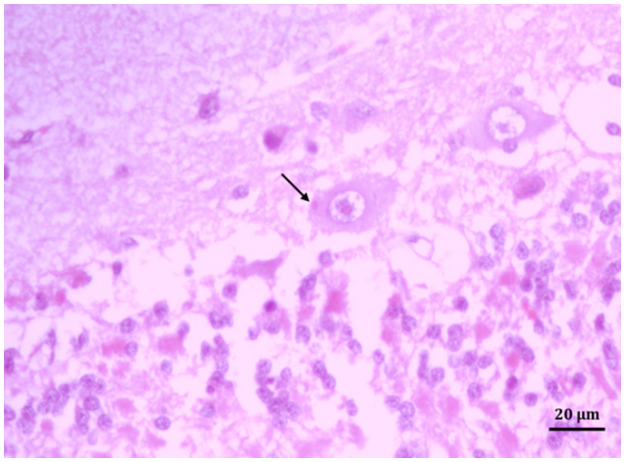

Figure 3. Cerebellum. Negri bodies (arrow) in Purkinje neurons cytoplasm in a horse. H&E.400×

There is no effective treatment for rabid animals or humans. Decision for treatment in this gelding was made because he was vaccinated, and trauma was the most likely differential. Later, therapeutic protocol was interrupted and euthanasia was chosen because of fast worsening of neurological signs (progressive paralytic form) along with lack of response to treatment and an obvious suffering by the gelding.

The decision for euthanasia in rabid horses is very controversial. According to Manning et al. (2008), a domestic animal (cat, dog or ferret) that bites a person should be confined and observed for 10 days. If it exhibits signs of rabies during this period, it should be euthanized immediately and tested for rabies (TEPSUMETHANON et al., 2004). No information is available regarding herbivores. Histological or dFAT diagnosis are easier in horses showing clinical signs for more than 4 days and so it is recommended to let the disease progress before euthanasia or let the animal die on his own (LIMA et al., 2005). However, World Organization for Animal Health recommends euthanasia in cases in which treatment is not feasible or recovery is unlikely (FRASER et al., 2013). So, euthanasia was the selected alternative for this case to minimize human risk (TOLOUEI; MOBARAK; MOSTOFI, 2017), and ensuring animal welfare.

Laboratory testing is essential for a definitive diagnosis of rabies, especially considering that clinical signs and gross postmortem lesions at necropsy are not considered pathognomonic in domestic animals (LIMA et al., 2005; BASSUINO et al., 2016). However, one of the main concerns of this case report was to obtain the most appropriate material for the correct diagnosis at necropsy. Inadequate collection can lead to misdiagnosis (DOGNANI et al., 2016) as most tests sensitivity

vary with the portion of the central nervous system tested (CARRIERI et al., 2006). A representative and adequately refrigerated sample of cortex, thalamus, hippocampus, cerebellum, brainstem, and spinal cord (cervical, thoracic, and lumbar) tissues were collected following recommendations of Ministério da Agricultura, Pecuária e Abastecimento (MAPA, Brazilian Ministry of Agriculture and Livestock) and sent to an authorized reference laboratory for rabies diagnosis (LACEN-BA). Although brain is the organ of choice, submission of medulla fragments in horses is recommended, as rabies virus antigen is particularly abundant in thalamus, pons and medulla (BINGHAM; van der MERWE, 2002; LIMA et al., 2005; CONSALES; BOLZAN, 2007; ACHKARD et al., 2010; BASSUINO et al., 2016).

Although dFAT test is considered highly sensitive and specific (between 96-99%) and currently the gold standard for postmortem rabies diagnosis recommended by WHO and World Organization for Animal Health (OIE, 2008; CONDORI et al., 2020), confirmation diagnosis can also be done through mice inoculation test or tissue culture and molecular tests (CONSALES; BOLZAN, 2007; LACKAY et al., 2008; TOLOUEI; MOBARAK; MOSTOFI, 2017). An immunohistochemical test is an important diagnostic aid tool when only formalin-fixed tissues are available (CONDORI et al., 2020). Other protocols, as RT-PCR or RT-qPCR LN34 Pan-Lyssavirus, are now considered acceptable tests for primary diagnosis but require special skills and are expensive (CONDORI et al., 2020). Biological tests are still considered one of the most accurate methods but can require at least 3 weeks for the final diagnosis (BASSUINO et al., 2016). They are indicated when skills and facilities for other tests are not available or results are inconclusive. Particularly in this case, dFAT tested negative twice, corroborating with previous studies in which false-negative results were observed in 20-44.5% of rabid horses (PEIXOTO; CUNHA; SACRAMENTO, 2000; PEDROSO et al., 2010). However, newborn mice inoculation test was positive. Discrepancies between tests are common in horses (PEIXOTO; CUNHA; SACRAMENTO, 2000, LIMA et al., 2005).

The remaining material was fixed and submitted to histopathology. Macroscopic lesions such as hemorrhage of white matter of the spinal cord (PEDROSO et al., 2010) were observed, although not specific for rabies. A perivascular inflammatory infiltrate was identified as well as Negri bodies, which are a hallmark for rabies diagnosis (BASSUINO et al., 2016; TOLOUEI; MOBARAK; MOSTOFI, 2017), but they are not found in all cases (LACKAY et al., 2008; COSTA et al., 2015). The rapid course of the disease in horses, usually with the animals dying in only 3-4 days may not allow sufficient time for histopathological lesions (COSTA et al., 2015). These inclusion bodies are less frequent in horses when compared do bovines (PEIXOTO; CUNHA; SACRAMENTO, 2000). In this horse, Negri bodies were found even with the animal being euthanized with 4 days of progression. Similar to the present case, characteristic Negri bodies were found in 64.28% of rabies cases in equids, mainly in the cervical spinal cord and in Purkinje neurons of cerebellum (PEDROSO et al., 2010).

This case report demonstrates that equine rabies must be considered in all clinical cases involving acute and progressive neurological signs, even in vaccinated animals, as it represents a potential source of contamination for humans. As the disease is always fatal in animals, use of PPE by the veterinarian team was essential to prevent contamination. PPE was used from the beginning of clinical care through the postmortem evaluation (TOLOUEI; MOBARAK; MOSTOFI, 2017). After the confirmation of rabies, the entire veterinary team was evaluated by an infectious disease specialist whom was responsible to determine the post-exposure prophylaxis.

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