ORIGINAL RESEARCH ARTICLE

Lethal infection by Herpes simplex virus 1 (HSV-1) in a captive Azara's Owl Monkey (*Aotus azarae*) in Paraguay

Infección letal por Herpes simplex virus 1 (HSV-1) en Marikiná de Azara (Aotus azarae) cautivo en Paraguay

Infecção letal pelo vírus Herpes simplex 1 (HSV-1) em Marikiná de Azara (Aotus azarae) em cativeiro no Paraguai

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Abstract

Anamnesis: A 2-year-old male *Aotus azarae* was brought to the wild animal clinic. The animal weighed 975 grams and was in poor body condition. The individual was kept in close contact with the caretakers, and it was fed to a large extent by the people in the household, sharing their meals. As reported by the caretaker, the animal was asthenic and anorexic since approximately 2 days ago. **Clinical and laboratory findings:** On clinical inspection, the animal was weakened, with pale oral mucosa and hyperemic pharynx, and a rectal temperature of 34.2°C. Dry crusts were observed in the perinasal region, and a slight dyspnea was perceived. The patient died during the inspection. The hemogram was suggestive of normocytic normochromic anemia, leukopenia, hypoproteinemia, and thrombocytopenia. The observed result of molecular analysis was detectable for HSV-1. **Conclusion:** Data obtained through anamnesis and clinical history, as well as hematologic findings and the PCR results, confirmed the diagnosis of HSV-1 infection. To the authors best knowledge, this is the first report of the disease in a non-human primate in Paraguay.

Keywords: *Anthropozoonosis; Aotus azarae; cross-transmission; Herpes simplex virus; Herpesvirus; HSV-1; New World primate; Owl monkey; PCR; Platyrrhini.*

Resumen

Anamnesis: Un *Aotus azarae* macho de 2 años fue llevado al Consultorio de Animales Silvestres. El animal pesaba 975 gramos y presentaba baja condición corporal. El individuo se mantenía en estrecho contacto con los cuidadores y era alimentado en gran medida por las personas de la casa, compartiendo sus comidas. Según informó el cuidador, el animal estaba asténico y anoréxico desde hacía aproximadamente 2 días. **Hallazgos clínicos y de laboratorio:** En la inspección clínica, el animal estaba debilitado, con la mucosa oral pálida y la faringe hiperémica, y la temperatura rectal de 34,2ºC. Se observaron costras secas en la región perinasal y se percibió una ligera disnea. El paciente falleció durante la inspección. El hemograma fue sugestivo de anemia normocítica normocrómica, leucopenia, hipoproteinemia y trombocitopenia. El resultado observado al análisis molecular fue detectable para VHS-1. **Conclusiones:** Los datos obtenidos a través de la anamnesis y la historia clínica, así como los

hallazgos hematológicos y los resultados de la PCR confirmaron el diagnóstico de infección por VHS-1. Según el entender de los autores, este es el primer reporte de la enfermedad en un primate no humano en Paraguay.
Palabras clave: *Antropozoonosis; Aotus azarae; Herpesvirus; Herpes simplex virus; HSV-1; Mono búho; PCR; Platirrino; primate del Nuevo Mundo; transmisión cruzada.*

Resumo

Anamnese: Um *Aotus azarae* macho de 2 anos de idade foi trazido para a clínica de animais selvagens. O animal pesava 975 gramas e estava em baixa condição corporal. O indivíduo estava em contato próximo com os cuidadores e era principalmente alimentado pelas pessoas da casa, compartilhando suas refeições. De acordo com o cuidador, o animal estava astênico e anoréxico há aproximadamente dois dias. **Achados clínicos e laboratoriais:** Na inspeção clínica, o animal estava debilitado, com mucosa oral pálida e faringe hiperêmica, e temperatura retal de 34,2ºC. Crostas secas foram observadas na região perinasal e uma leve dispneia foi percebida. O paciente morreu durante a inspeção. O hemograma foi sugestivo de anemia normocítica normocrômica, leucopenia, hipoproteinemia e trombocitopenia. O resultado observado na análise molecular foi detectável para HSV-1. **Conclusões:** Os dados obtidos na anamnese e na história clínica, bem como os achados hematológicos e os resultados da PCR confirmaram o diagnóstico de infecção pelo HSV-1. Para o conhecimento dos autores, este é o primeiro relato da doença em um primata não humano no Paraguai.
Palavras-chave: *Antropozoonose; Aotus azarae; Herpesvírus; HSV-1; Macaco coruja; PCR; Platirrino; Primata do Novo Mundo; transmissão cruzada; Vírus herpes simplex.*

Introduction

Herpesviruses are enveloped DNA viruses with complex genomes that infect a wide variety of vertebrate species, with many primates and humans being natural hosts (Ludlage and Mansfield, 2003; Casagrande, 2014). Formerly classified within the family Herpesviridae, now in three families within the Order Herpesvirales: the family Herpesviridae, which retains all mammalian, avian and reptile herpesviruses; the new family Alloherpesviridae, comprising fish and frog viruses; and the new family Malacoherpesviridae, containing the viruses of bivalves. The family Herpesviridae is again divided into three subfamilies, among which are the 39-known species of human and non-human primate Herpesviruses (Casagrande, 2014).

The genus *Simplexvirus*, of the subfamily Alphaherpesvirinae, contains five species of New World Primate herpesviruses (NWP), as well as two species of human herpesviruses: *Herpes*

simplex virus 1 (HSV-1) and *Herpes simplex virus* 2 (HSV-2). Many human and non-human primates carry their own species of Herpesviruses of this genus, which normally do not cause clinical disease in the immunocompetent natural host (Casagrande, 2014). Humans are the only primate species infected by two distinct herpes simplex viruses: HSV-1 and HSV-2 (Wertheim *et al.*, 2014). Herpesviruses have been infecting and co-diverging with their vertebrate hosts for hundreds of millions of years (Wertheim *et al.*, 2014), however, when these viruses infect different primate species, they can cause significant and often fatal clinical disease (Casagrande, 2014).

Unlike Old World Primates (OWP), which have a generally self-limiting infection, like infection in humans, NWPs are more susceptible to HSV-1 infection, usually developing a generalized and fatal disease, characterized by anorexia, dermatitis, pruritus, depression, and ulcerative lesions in the oral cavity and gastrointestinal tract (Casagrande, 2014; Fortman *et al.*, 2018). The disease produced by these viruses has already been described in captive NWPs of the genus *Cebus* (Zinsser, 1929; Souvignet, 2019), *Aotus* (Katzin, 1967; Barahona *et al.*, 1976; Meignier *et al.*, 1990; Gozalo *et al.*, 2008; Kreutzer *et al.*, 2011), *Callithrix* (Huemer *et al.*, 2002; Mätz-Rensing *et al.*, 2003; Hatt *et al.*, 2004; Casagrande, 2007; Sekulin *et al.*, 2010; Imura *et al.*, 2014; Araújo *et al.*, 2016), and *Pithecia* (Schrenzel *et al.*, 2003; Lapid and Eshar, 2017). Primates of the genus *Aotus* are known for their high susceptibility to HSV infection, in whom the virus apparently has a predilection for the cerebral cortex, causing encephalitis (Calle and Joslin, 2015), which is why they are also used as a model for the study of the pathogen (Katzin *et al.*, 1967; Todo *et al.*, 2000; Roth *et al.*, 2014).

Because of the frequent but unapparent spread of herpesviruses, careful handling of the animals should be recommended, and certain hygienic restrictions should be applied for the sake of both owners and pet monkeys, whereas standard veterinary practice is to consider whether diseases of primates that have been in close contact with humans may have been caused by human viruses (Huemer *et al.*, 2002). In addition to considering the transmission of NWP Herpesviruses, such as CeHV-1, to a human host, where it can develop potentially fatal encephalitis (Casagrande, 2007), the potential link between a wild animal and an acquired infection from a human host should be highlighted, considering that humans in contact with the animal will not necessarily demonstrate signs of disease (Huemer *et al*, 2002) because herpesviruses do not usually cause serious infections in healthy members of their natural host species, as most of these infections are asymptomatic (Eberle and Jones-Engel, 2017). A distinctive feature of herpesviruses is their ability to establish latent infections that persist throughout the life of the host without clinically apparent signs of infection (Eberle and Jones-

Engel, 2017). The objective of the present work is to report a case of lethal infection by *Herpes simplex virus* 1 (HSV-1) in a captive Azara's owl monkey (*Aotus azarae*) in Paraguay.

Patient Examination

Anamnesis

A 2-year-old male pet *Aotus azarae* was brought to the Wild animal clinic in the Faculty of Veterinary Sciences, National University of Asunción. The animal weighed 975 grams and was in poor body condition. The individual was kept in close contact with the caretakers: either loose inside the house or tied at waist level with a nylon leash and on the caretakers' shoulders; and it was fed to a large extent by the people in the household, sharing their meals, even practicing mouth-to-mouth feeding. As reported by the caretaker, the animal was asthenic and anorexic since approximately 2 days ago.

Clinical findings

On clinical inspection, the animal was observed weakened, with pale oral mucosa and hyperemic pharynx, and a rectal temperature of 34.2°C (hypothermia). Dry crusts were observed in the perinasal region, and a slight dyspnea was perceived. The patient was placed in an oxygenation chamber and died after one hour.

Diagnostic aids used

Immediately after confirming the death of the animal, 3 ml of blood was extracted by cardiac puncture. Of the blood extracted, 1 ml was placed in a vial with EDTA, for a hemogram, and 2 ml in a vial without anticoagulant, for molecular diagnostics, and both were refrigerated at 4°C until processing. The caretaker refused to send the patient’s body for routine post-mortem studies.

The blood sample for hemogram was processed by the following methods: (a) Counting of figured elements and hemoglobin by manual methods; (b) Differential counting of leukocytes in blood smears with Giemsa staining; (c) Morphological evaluation of blood cells in blood smears with Giemsa staining; (d) Determination of total plasma protein level by refractometry. The results, shown in Table 1, were suggestive of normocytic normochromic anemia, leukopenia, hypoproteinemia, and thrombocytopenia, being indicative of viremia.

Table 1. Hematological results from a sample taken from an *Aotus azarae* infected by HSV-1.

Analyte (unit)	Results	Reference*
Hematocrit (%)	24.0	34.1 – 53.6
Hemoglobin (g/100 ml)	8.6	12.0 – 19.4
Red blood cells (10^6/mm^3)	3.2	4.56 – 7.06
Mean corpuscular volume (fl)	75	71 – 83
Mean corpuscular hemoglobin (pg)	26	23 – 30
Mean corpuscular hemoglobin concentration (gr/dl)	35	32 – 39
White blood cells (10^6/mm^3)	4300	4900 – 21000
Segmented (µ/l)	989	910 – 7190
Lymphocytes (µ/l)	3311	3140 – 10600
Monocytes (µ/l)	--	0 – 302
Eosinophils (µ/l)	--	94 – 4062
Basophils (µ/l)	--	0 – 411
Platelets (10^3/µl)	2.0	3.7 – 24.5
Total proteins (g/L)	4.2	6.9 – 8.1

*Takeshita *et al*. (2011)

From the blood sample, RNA extraction was performed with the commercial kit Ribospin vRD (GeneAll), following the manufacturer's instructions. The primers used for HSV-1 detection: HSV-1 Forward: 5' GCAGTTTACGTACAACCACATACAGC 3', Reverse: 5' AGCTTGCGGGCCTCGTT 3' and the probe: CGGCCCAACATATCGTTGACATGGC. The primers used for HSV-2 detection: Forward: 5' TGCAGTTTACGTATAACCACATACAGC 3', Reverse: 5' AGCTTGCGGGCCTCGTT 3' and the probe: CGCCCCAGCATGTCGTTCACGT. The conditions used in the BioRad CFX96 thermal cycler were: Activation: 95°C for 2 minutes, then 40 cycles of denaturation: 95°C, for 5 seconds and, finally, 60°C extension for 20 seconds. The observed result was detectable for HSV-1, and not detectable for HSV-2.

Discussion

Given that humans and nonhuman primates (NHPs) are genetically and physiologically similar, it is not surprising that some herpesviruses from NHPs can infect humans, and vice versa.

Although most of these cross-species infections are probably abortive (i.e., the virus cannot complete its replicative cycle to produce an active or latent infection or cause clinically apparent disease), some herpesviruses produce severe or lethal infections when transmitted to a non-natural host species (Eberle and Jones-Engel, 2017).

The clinical signs reported in captive primates of the genus *Aotus* infected with HSV-1 partially coincide with the case reported in the present work, mentioning severe dyspnea, apathy, hypothermia and lethargy that gradually worsened until the death of the animal in a period of 4 to 7 days (Melendez *et al.*, 1969; Kreutzer *et al.*, 2011). Reports also mention lesions in the oral cavity, including vesicles, mucous exudate, necrotic plaques, moderate multifocal gingival defects, and ulcers in the oral mucosa and tongue, which may extend into the pharynx, esophagus, and trachea (Melendez *et al.*, 1969; Gozalo *et al.*, 2008; Kreutzer *et al.*, 2011). All cases report infection with high case fatality (Melendez *et al.*, 1969; Meignier *et al.*, 1990; Gozalo *et al.*, 2008; Kreutzer *et al.*, 2011).

In *Callithrix* spp. another group of NWPs, an acute course of infection is also reported, with an evolution between 1 to 8 days (Juan-Sallés *et al*., 1997; Huemer *et al.*, 2002; Mätz-Rensing *et al.*, 2003; Hatt *et al.*, 2004; Casagrande, 2007). Clinical signs are similar, reporting prostration, paresis, hyporexia, hypersalivation, vomiting, diarrhea, aggressiveness, seizures, nystagmus, anisocoria, and dyspnea (Huemer *et al*., 2002; Hatt *et al.*, 2004; Casagrande, 2007; Imura *et al.*, 2014). Associated with the neurological signs, most animals present small ulcers covered by crusts on the skin of the face, extensive ulcers covered by whitish fibrinous material on the oral mucosa and tongue, and conjunctivitis may occur (Mätz-Rensing *et al*., 2003; Hatt *et al*., 2004; Casagrande, 2007; Sekulin *et al.*, 2010; Araújo *et al*., 2016). Some animals present neurological alterations without skin and mucosal lesions (Juan-Sallés *et al*., 1997; Casagrande, 2007; Imura *et al.*, 2014), or do not present clinical manifestations, being found dead (Mätz-Rensing *et al.*, 2003; Hatt *et al.*, 2004; Casagrande, 2007). In *Pithecia pithecia*, outbreaks of acute and fatal infection have also been reported, with animals dying between 48 and 96 hours after the onset of signs, being similar to the cases in *Aotus* spp. and *Callithrix* spp. (Schrenzel *et al.*, 2003; Lapid and Eshar, 2017).

In terms of diagnostic methods, the use of serological testing for the diagnosis of herpesvirosis should be approached with caution because many primates are asymptomatic carriers of various species of herpesviruses. When histopathological examinations are performed, alterations are non-suppurative meningoencephalitis with necrotizing vasculitis, and the presence of typical intranuclear inclusions, although it does not allow determination of the species of herpesvirus. In contrast, if immunohistochemistry is performed using monoclonal antibodies, it is possible

to differentiate several species, although antiHSV-1 and antiHSV-2 antibodies are polyclonal and cross-labeled with each other (Casagrande, 2014).

Currently, PCR is the technique of choice for the definitive diagnosis of the herpesvirus species involved in diseases of humans and NHPs, although the use of the technique must be associated with the clinical presentation and lesions of the patient. Swabs of lesions or blood from diseased animals can be used, as well as organs obtained during necropsy (Casagrande, 2007; Casagrande, 2014). The reports by Schrenzel *et al.* (2003), Casagrande (2007), and Sekulin *et al.* (2010) present the primers used for the detection of HSV-1 in *Pithecia pithecia* and *Callithrix jacchus* specimens, respectively.

Treatment with acyclovir does not prevent death from encephalitis in HSV-1-infected animals, although it remains the antiherpetic drug of choice in humans (Casagrande, 2014; Kukhanova *et al*., 2014). Other drugs used in humans are valacyclocir and ganciclovir, which could be used in NHPs (Casagrande, 2014). There is a single report of a *Callithrix jacchus* that survived a natural HSV-1 infection, and recovered spontaneously without any treatment (Hatt *et al*., 2004). It should be noted that HSV-1 infection in NHPs is an anthropozoonosis, and the present report coincides with acute spontaneous HSV-1 infections described in fatal cases in *Aotus* spp. and *Callithrix* spp. after contact with a person carrying HSV-1 (Mätz-Rensing *et al.*, 2003), kept as a pet in close contact with the owners (Juan-Sallés *et al.*, 1997; Huemer *et al.*, 2002; Hatt *et al.*, 2004; Kreutzer *et al.*, 2011; Imura *et al.*, 2014), or even sharing food with the animal (Araújo *et al.*, 2016). HSV-1 infection in NWPs has already been widely reported in Brazil, being observed in animals from zoos, conservation and breeding centers, research centers, as well as cases reported by veterinarians in pet patients, but mainly in primates of the *Callithrix* genus (Casagrande, 2007). A work conducted in Peru with primates kept in homes reports that 50.4% go for consultation with an infectious disease, and 11.4% go for an infectious and non-infectious disease at the same time (Nolasco, 2017), highlighting the potential impact of household primate ownership on public health.

Conclusions

Data obtained through anamnesis and clinical history, as well as observable signs during the physical examination, the hematologic findings, and the PCR results confirmed the diagnosis of HSV-1 infection that caused the death of a captive Azara's owl monkey. To the authors best knowledge, this is the first report of the disease in a non-human primate in Paraguay.

Declarations

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Conflicts of interest

The authors declare they have no conflicts of interest regarding the work presented in this report.

Author contributions

J. Richard Vetter: study conception, data collection, wrote the paper. Marlene Florentín-Morel: data collection, critical review of the paper. MaríaGraciela Riera-Domínguez: data collection, wrote the paper. Ricardo G. Cañiza: data collection, critical review of the paper.

Use of artificial intelligence (AI)

No AI or AI-assisted technologies were used during the preparation of this work.

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