Case Report

Management of Ocular *Human herpesvirus 1* Infection in a White-faced Saki Monkey (*Pithecia pithecia*)

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A 20-y-old male intact white-faced saki monkey (*Pithecia pithecia*) presented with an acute ocular disease of the right eye. Clinical signs included periocular swelling, conjunctivitis, and anisocoria with a miotic right pupil. Conjunctival swabs were positive for *Human herpesvirus 1* (HHV1) according to PCR amplification with sequencing. Initial clinical signs resolved with supportive treatment, and the animal was managed chronically by using acyclovir (5 mg/kg PO twice daily) during flare-ups. After more than 2 y, the progression of clinical disease led to enucleation of the right eye. At 2 mo after surgery, acute presentation of severe neurologic signs, including ataxia and blindness, resulted in euthanasia. Histopathology, PCR analysis, and sequencing results were consistent with viral encephalitis due to HHV1; coinfection with *Pithecia pithecia lymphocryptovirus 1* was identified. This report describes the first case of managed HHV1 infection in a platyrrhine primate and the first case of HHV1 in a white-faced saki monkey that was not rapidly fatal.

Abbreviation: HHV1, *Human herpesvirus 1*; PpLCV1, *Pithecia pithecia lymphocryptovirus 1*

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Human herpesvirus 1 (HHV1) is an alphaherpesvirus in the genus *Simplexvirus* that has high pathogenicity in NHP and other Euarchontoglires. In the endemic host, humans (*Homo sapiens*), HHV1 infection is lifelong and usually causes subclinical infection, with a prevalence of more than 98% in otherwise healthy adults.¹⁴ However, cold sores occur in some people, and severe fatal encephalitis is possible in otherwise healthy neonates.¹⁹ The virus–host range is widespread across Euarchontoglires, the mammalian superorder containing primates, rabbits, and rodents.²² A diverse array of nonhuman Euarchontoglires are susceptible to systemic HHV1 disease (typically encephalitis), especially in the case of young or immunocompromised animals.^{12,15–17,31,32} The parvorder Catarrhini contains humans and other primates native to the Old World. The other clade in the infraorder Simiiformes, the parvorder Platyrrhini, contains the primates native to the New World. Platyrrhini are heavily represented in the pet trade and in the literature regarding non-human HHV1 disease. Rapidly fatal disease associated with acute encephalitis has been reported in black howler monkeys (*Alouatta caraya*), owl monkeys (*Aotus* spp.), marmosets (*Callithrix* spp.), and white-faced saki monkeys (*Pithecia pithecia*).^{2,10,18,20,24} However, some reports of HHV1 in platyrrhines have indicated differences in susceptibility among species and subjects.^{8,29} Experimental corneal infection with HHV1 in capuchin monkeys

(*Cebus apella*) and squirrel monkeys (*Saimiri sciureus*) produced corneal disease in both species, but subsequent systemic disease was not reported.^{8,29} Interestingly, capuchin monkeys have also been reported to be asymptotically infected with *Macacine herpesvirus 1*, another *Simplexvirus* endemic in a catarrhine host, rhesus macaques (*Macaca mulatta*).⁶ In a naturally occurring outbreak of HHV1 in owl monkeys, some animals developed rapidly fatal encephalitis, whereas others showed only mild signs limited to dyscoria and posterior synechia.¹⁰ All owl monkeys that did not die in the outbreak were euthanized, so the long-term outcome was not determined.¹⁰ Prolonged management of HHV1 disease in a platyrrhine has not been reported previously.

Case Report

A 20-y-old male, intact, captive white-faced saki monkey (*Pithecia pithecia*) with an acute history of right periocular swelling and lethargy was anesthetized for a complete physical examination. This animal's prior medical history included chronic proteinuria and diarrhea, which were managed by using benazepril (0.5 mg/kg PO daily; Diamondback Drugs, Scottsdale, AZ), flaxseed oil (50 mg/kg PO daily; Puritan's Pride, Holbrook, NY), and metronidazole (5 mg/kg PO daily; Wedgewood Village Pharmacy, Swedesboro, NY).

On initial physical examination under anesthesia, findings included right-sided periocular lid swelling, conjunctival hyperemia and edema, mucoid discharge, corneal edema, a 3×2-mm central corneal ulcer, and anisocoria with a miotic right pupil. Oral examination revealed erythematous gingiva and 2 thick, off-white plaques on the tip of the tongue. In addition, a low

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body condition score (3 on a scale of 9) and 15% weight loss over the preceding 19 d prior were noted.

CBC analysis, serum biochemistry, and urinalysis revealed leukocytosis ($19.8 \times 10^3/\mu\text{L}$; reference range, 3.7 to $19.11 \times 10^3/\mu\text{L}$), neutrophilia ($13.9 \times 10^3/\mu\text{L}$; reference range, 1.5 to $11.96 \times 10^3/\mu\text{L}$), monocytosis ($4.4 \times 10^3/\mu\text{L}$; reference range, 0.053 to $1.211 \times 10^3/\mu\text{L}$), hypoalbuminemia (2.2 g/dL; reference range, 2.4 to 5.9 g/dL), proteinuria ($4+$, UPC 9.97), hematuria (0 to 2 RBC per high-power field), pyuria (1 to 3 WBC per high-power field), and mild bacteriuria.²⁷ Liver enzymes including ALT (3 U/L; reference range, 3 to 37 U/L), AST (45 U/L; reference range, 20 to 123 U/L), and GGT (31 U/L; reference range, 7 to 61 U/L) were unremarkable.²⁷ However, total bilirubin was not included in the chemistry panel. A urine culture was negative. Whole-body radiographs, abdominal ultrasonography, cytology of a scraping of the tongue, and lead II electrocardiography were unremarkable. Treatment administered at the time of the examination included lactated Ringer solution (45 mL/kg SC; Hospira, Lake Forest, IL), penicillin G benzathine and penicillin G procaine ($22,000$ IU/kg SC; Bimeda, La Sueur, MN), ivermectin (0.4 mg/kg SC, Merial Limited, Duluth, GA), meloxicam (0.2 mg/kg SC, Norbrook Laboratories Limited, Northern Ireland), ceftiofur crystalline free acid (10 mg/kg SC, Zoetis, Kalamazoo, MI), and neomycin, polymyxin B sulfates, and bacitracin zinc ophthalmic ointment (topically on right eye, Bausch and Lomb, Tampa FL). Treatment courses of tramadol (1.2 mg/kg PO twice daily for 9 d; Diamondback Drugs) and azithromycin (10 mg/kg PO daily for 7 d; Greenstone, Peapack, NJ) were initiated, and ciprofloxacin (10 mg/kg PO twice daily for 24 d; Bayer HealthCare, Whippany, NJ) was initiated 5 d later.

At 10 d after the initial presentation, a recheck examination of the monkey under anesthesia revealed persistent ocular abnormalities, including a 3×5 -mm corneal ulcer of the right eye. In addition, mucoid discharge was present in the left eye. To promote corneal healing, a complete temporary tarsorrhaphy of the right eye was performed by using $5-0$ polydioxanone suture in a horizontal mattress pattern. In addition, exudative abrasions and ulcerations were present on the right arm and the face above each eye, on the chin, and on the right cheek. Cytologic evaluation of impression smears of the affected areas revealed severe neutrophilic and histiocytic inflammation. Treatments during the examination included penicillin G benzathine and penicillin G procaine ($22,000$ IU/kg SC), meloxicam (0.2 mg/kg SC), gentamicin (0.05 mL, 100 mg/mL, subconjunctival right eye; VetOne, Boise, ID), lactated Ringer solution (30 mL/kg SC), and nystatin-neomycin sulfate-thiostrepton-triamcinolone ointment (topically on the right wrist; Animax, Dechra, Overland Park, KS), and the scabs and wounds were clipped and cleaned with chlorhexidine solution (Vetoquinol USA, Fort Worth, TX). Due to concern about an underlying viral infection, serum was submitted for serology to VRL Laboratories (San Antonio, TX); the results were negative for *Saimiriine herpesvirus 4*, *Saimiriine herpesvirus 2*, *Saimiriine herpesvirus 1*, HHV1, *Human herpesvirus 2*, HHV1 IgM, *Human herpesvirus 2* IgM, and measles, as determined by previously reported methods.¹¹ A swab collected from the corneal and subconjunctival surfaces of the right eye was positive for HHV1 by PCR amplification with sequencing (University of Tennessee, Knoxville, TN) according to previously reported methods.²⁸ Treatment courses of nystatin-neomycin sulfate-thiostrepton-triamcinolone ointment (topically on right carpus twice daily for 5 d; Animax, Dechra), cephalexin (22 mg/kg PO twice daily for 17 d; Hospira), meloxicam (0.1 mg/kg PO once daily for 10 d), and acyclovir (5 mg/kg PO twice daily for 24 d; Diamondback Drugs) were

Figure 1. Photomicrograph of the frontal cerebrum of a 22-y-old saki monkey, showing marked expansion of the leptomeninges by mixed inflammatory cells, with lymphocytes predominating. Inflammatory infiltrates extend into the cerebrum forming perivascular cuffs. Vasculature is congested, and there is frequent perivascular hemorrhage into the neuropil with attendant necrosis, vacuolation, and inflammation. Hematoxylin and eosin stain; magnification, $40\times$.

Figure 2. Photomicrograph of the frontal cerebrum of a 22-y-old saki monkey, showing degenerate neutrophils and karyorrhectic debris surrounding vessels and infiltrating the neuropil. Neuronal nuclei contain indistinct basophilic (open arrows) or distinct eosinophilic (solid arrow) inclusions with margination of chromatin. Morphology of the inclusions is characteristic of herpesvirus. Hematoxylin and eosin stain; magnification, $400\times$.

initiated. Additional treatments at a recheck examination 8 d later included removal of the temporary tarsorrhaphy sutures, gentamicin (0.1 mL subconjunctivally in right eye, with 0.05 mL in lower lid and 0.05 mL in upper lid), meloxicam (0.2 mg/kg IM), ceftiofur sodium crystalline free acid (7.5 mg/kg SC), and lactated Ringer solution (30 mL/kg SC). Additional medications included L-lysine (12.5 mg/kg PO daily; Carlson, Arlington Heights, IL); acyclovir, cephalexin, ciprofloxacin, and meloxicam were continued.

A recheck examination 25 d after the initial presentation showed no evidence of corneal ulceration. At that time, the right eye was considered nonvisual, with evidence of mild corneal degeneration, a narrow anterior chamber, and an active pupillary light response. Oral administration of L-lysine was

Figure 3. Representative region of DNA sequence chromatogram of panherpesviral DNA polymerase gene PCR product from the brain tissue of a 22-y-old saki monkey. Guanine is in black, adenine is in green, cytosine is in blue, and thymine is in red. Sequences for *Human herpesvirus 1* (GenBank accession no. KX424525) and *Pithecia pithecia lymphocryptovirus 1* (GenBank accession no. AY139025) are below the chromatogram. Note that when one of these sequences is subtracted from the chromatogram, the other is present.

continued. In addition, the skin lesions had resolved at that time.

There were no additional concerns until 6 mo after the initial presentation, when a recheck exam showed moderate conjunctival hyperemia of the left eye. A swab of this eye was positive for HHV1 on PCR analysis, indicating viral shedding at this time. Acyclovir treatment was reinitiated. Three additional flare-ups of periorcular pruritus and conjunctivitis were treated with courses of acyclovir over the 2 y 3 mo after the initial presentation.

Approximately 2 y 4 mo after the initial presentation, the right eye was enucleated due to concerns of recurring ocular disease. L-Lysine was discontinued approximately 1 wk later, in light of removal of the affected eye and worsening patient compliance. Histology of the affected eye revealed chronic, erosive keratoconjunctivitis; mild to moderate, chronic, lymphohistiocytic iridocyclitis with multiple synechia; and chronic retinal degeneration and detachment. No viral inclusions were found.

Two months after enucleation, this animal became acutely ataxic, obtunded, and blind. Euthanasia was elected owing to the suspected progression of HHV1-associated disease. Histopathology confirmed disseminated disease consistent with herpesvirus, including severe, multifocal to coalescing necrohemorrhagic meningoencephalitis with neuronal intranuclear inclusion bodies (Figures 1 and 2). The bilateral optic and trigeminal nerves and the left eye were infiltrated by lymphocytes and plasma cells. Other findings included mild lymphohistiocytic hepatitis, mild lymphoplasmacytic interstitial nephritis, mild lymphocytic gastroenteritis, moderate mucopurulent to lymphocytic laryngitis, mild lymphocytic conjunctivitis of the left eye, and granulomatous inflammation of the enucleation site of the right eye.

Brain tissue was submitted to the University of Florida for confirmation of HHV1 by PCR and sequencing analysis. DNA was extracted (DNeasy, Qiagen, Valencia, CA) from brain tissue. Extraction of DNA-free water was used as a negative control. Nested PCR amplification was performed by using previously described consensus primers for the herpesviral DNA-dependent DNA polymerase gene.²⁸ The PCR amplicon was resolved in a 1.5% agarose gel, excised, purified (QIAquick Gel Extraction Kit, Qiagen), sequenced according to the Sanger method by using a Big-Dye Terminator Kit (Applied Biosystems, Foster City, CA), and analyzed on ABI 3130 automated DNA sequencers. Sequencing (Genewiz, South Plainfield, NJ) yielded dual peaks at most nucleotides, consistent with a mixed sequence (Figure 3). The sequence obtained was compared with sequences in the GenBank databases (National Center for Biotechnology Information, Bethesda, MD), EMBL (Cambridge, United Kingdom), and the Data Bank of Japan (Mishima, Shizuoka, Japan) by

using BLASTN.¹ The BLASTN search found closest sequence homology with HHV1 (GenBank accession no. KX424525). When peaks matching HHV1 were subtracted, the sequence of the remaining peaks showed 100% homology with *Pithecia pithecia lymphocryptovirus 1* (PpLCV1; GenBank accession no. AY139025), previously reported from the lung of a captive white-faced saki monkey in Germany.⁷ Use of fluorescence peak heights associated with different nucleotides to assess nucleotide polymorphisms has been validated, and the dominance of HHV1 suggests it likely was present in greater copy numbers than PpLCV1.¹³ Therefore, sequencing analysis confirmed the presence of HHV1 in the brain tissue of this saki monkey.

Discussion

This report is the first description of the management of a platyrrhine with HHV1, and the first report of HHV1 in a white-faced saki monkey that was not rapidly fatal. Treatment for the animal in this case was aimed at reducing shedding and consisted of acyclovir given during times of suspected increased shedding. L-lysine was administered also but has not been found efficacious for control of herpesviral disease and is considered unlikely to have played a role in this case.^{3,5} Oral acyclovir and oral valacyclovir have both been shown to be effective for treatment of HHV1, although the long-term efficacy of these therapies is uncertain.⁵ A survival time of 2.5 y has not been reported previously for this species or other platyrrhines, perhaps reflecting a lack of antemortem diagnostics in previous cases. Previous cases of identified infection without rapid fatality have been reported in other platyrrhines.^{8,10,29} Antemortem diagnostic investigation is indicated in platyrrhines with ocular inflammatory disease.

Proteinuria detected at the time of the saki monkey's initial presentation was similar to previous findings in this animal and were likely due to suspected glomerular protein loss first diagnosed 3 y prior to the ocular findings. Ultrasonography with a consulting radiologist at the time of initial diagnosis of proteinuria revealed mild pyelectasia bilaterally and prominent vasculature in the left renal pelvis (diameter, 5 mm). Clinical response to benazepril and flax seed oil was varied over the clinical course but ultimately did not completely control protein loss. Chronic renal disease was confirmed on necropsy findings. Other causes of proteinuria such as low-grade herpes meningitis cannot be ruled out completely, because no spinal tap was performed.

At the time of serologic testing in this animal, there was no evidence of seroconversion. Previous cases of HHV1 in white-faced saki monkeys have also been negative for antibodies to HHV1.²⁴ The negative serologic response may be due to lack of cross-species serologic reactivity when using antihuman

secondary antibodies to detect antibodies in white-faced saki monkeys. Other platyrrhini have shown evidence of serologic response, but whether these responses are due to species differences or to differences in testing methods is unknown.^{8,10} In the case we present here, testing used a rapid-dot immunobinding assay, whereas the other reported tests yielded positive results in platyrrhini have used serum neutralization or ELISA.^{8,10,11} Alternatively seroconversion might have occurred after testing in the presented case, but additional serologic testing was not done.

It is unknown what triggered the final progression of the disease in this case. Although low-level meningitis might have been present earlier, the hemorrhage and necrosis observed on histopathology indicated acute progression, and it is consistent with the observed normal mentation and mobility until immediately prior to death. Although white-faced saki monkeys have been documented to live until 36 y of age, a more typical lifespan in the wild is 15 y.³⁰ At 22 y of age, this animal was geriatric, and reactivation of HHV1 has been associated with age.²⁵

The role of *Pithecia pithecia lymphocryptovirus 1* in the presented case is unknown. Lymphocryptoviruses are gammaherpesviruses, and unique lymphocryptoviruses have been identified in at least 42 NHP species. These viruses are generally considered to be host-adapted; however, fatal lymphoproliferative disease was associated with the lymphocryptovirus *Callitrichine herpesvirus 3* in a group of common marmosets (*Callithrix jacchus*).^{21,23} In addition, intranuclear inclusions similar to those seen in our case have been identified in rhesus macaques infected with *Macacine herpesvirus 4*, another lymphocryptovirus,⁴ but the role of *Pithecia pithecia lymphocryptovirus 1* in disease has not been investigated.²¹ In addition, the repeated positive PCR tests for HHV1 during the course of our animal's disease and the similarities in final clinical course to other cases of white-faced saki monkeys suggest that HHV1 was the cause of ocular disease and ultimate meningoencephalitis in our case.^{18,24}

Because reactivation of HHV1 has been associated with coinfection with other herpesviruses, the presence of the lymphocryptovirus might have contributed indirectly to worsening of clinical disease.²⁵ CNS coinfection with HHV1 and the human lymphocryptovirus *Human herpesvirus 4* has been reported.²⁶ Coinfection with HHV1 and *Human herpesvirus 4* results in significantly altered production of cytokines by cultured lymphocytes compared with single infection with either virus.⁹ Cytokines have a significant effect on the course of infectious disease.

At the time of the initial presentation, the saki monkey in this case report shared an enclosure with a female white-faced saki monkey and 2 golden lion tamarins (*Leontopithecus rosalia*). Because of concern about their exposure to HHV1, these animals were subsequently housed separately from the male saki monkey and underwent examinations for diagnostic testing. All 3 animals were negative for HHV1 by serology and PCR testing and never exhibited clinical signs of disease consistent with HHV1. Although we assume that these exhibit-mates are susceptible to the disease, the close contact required for transmission perhaps did not occur. In another case, a family of white-faced saki monkeys with HHV1 resulted in the death of all 3 saki monkeys, but 5 white-lipped tamarins (*Saguinus labiatus*) in the same enclosure never developed clinical illness.¹⁸

When deciding to treat a captive platyrrhine for HHV1, it is important to consider the health of other animals in the collection because the disease has been reported to affect multiple animals.^{10,18,20,24} In the presented case, this saki monkey was housed separately to reduce risk to other animals. However, housing

a social primate alone has long-term implications for quality of life. Such concerns may be partially mitigated by allowing visual contact with other animals or providing additional enrichment. This decision should be made on a case-by-case basis.

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