UNIVERSIDADE DE BRASÍLIA
FACULDADE DE AGRONOMIA E MEDICINA VETERINÁRIA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS ANIMAIS

PATHOLOGICAL INVESTIGATION OF INFECTIOUS DISEASES IN FREE- RANGING BLACK-TUFTED MARMOSETS (*Callitrix penicillata*) AND IMPLICATIONS FOR PUBLIC HEALTH AND CONSERVATION IN BRAZIL

TAIS MEZIARA WILSON

TESE DE DOUTORADO EM CIÊNCIAS ANIMAIS

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CONTENTS

FIGURES LIST

Chapter 2

Chapter 3

10x). B: Intranuclear inclusion bodies in epithelial cells at the margin of the lesion and multinucleated syncytial cell (arrow) (HE, original magnification 40X). C: HSV-1 immunostaining within epithelial cells in the area of necrotizing glossitis (IHC, original magnification 40x). D. Epithelial cell containing accumulations of herpesvirus within the cytoplasm, scale bar: 600 nm. Inset: higher magnification image of herpesvirus particles with well-defined tegument layer in the cytoplasm, scale bar: 400 nm, transmission electron microscopy.

Figure 5: Liver pathology in free-ranging black-tufted marmosets with fatal human herpes simplex virus-1 (HSV-1) infection. A) Intranuclear inclusion bodies in hepatocytes at the margin of a necrotic focus (HE, original magnification 63x), B) and multinucleated syncytial cell (arrow) (HE, original magnification 63x). C) HSV-1 immunostaining within hepatocytes in an area of necrotizing hepatitis (IHC, original magnification 40x). D) Herpesvirus in the cytoplasm of a hepatocyte, scale bar: 400 nm, transmission electron microscopy.

TABLES LIST

Chapter 2

Chapter 3

ABSTRACT

Several emerging infections that became epidemic in humans have originated in non-human primates (NHPs). These disease transmission events can be driven by man-made alterations to animal habitats and are essential for a One Health viewpoint. Etiologic agents of fatal infectious diseases can be diagnosed laboratory testing of tissues, as such necropsy is key for improving recognition of emerging and re-emerging infectious diseases. Most of the studies of infectious diseases in NHPs are based on serological or molecular assays, there are limited data on infectious diseases as the cause of deaths in NHPs in Brazil. Natural fatal infectious diseases as a cause of death were investigated in the Veterinary Pathology Laboratory at the University of Brasilia as part of the National Surveillance Program of Yellow Fever Epizootics in NHP of the Brazilian Ministry of Health. This investigation leading to the identification of other fatal infectious diseases in NHPs; herein we describe, from 1,042 cases retrieved, histopathological, immunohistochemical, molecular diagnosis, and epidemiological investigation of fatal *Leptospira interrogans* infection in an urbanized, free-ranging, black-tufted marmoset (*Callithrix penicilatta*) in Brazil. Fatal leptospirosis in NHPs is rare, this is the first report of fatal leptospirosis in a free-ranging NHP describing findings essential to facilitate the postmortem diagnosis of leptospirosis and understanding the disease in NHP. Applying the One Health perspective brings into consideration the possible role of NHPs in the epidemiology and transmission dynamics of human and animal leptospirosis, and potential of pathogen spillover at the human-NHP interface in anthropized areas. NHP are important sentinels for some zoonotic diseases in Brazil, and these animals could also indicate leptospirosis risks in the environment. Another aspect on the One Health perspective is reverse zoonoses, where human diseases can be spread to vulnerable wildlife populations. This is a concern for marmoset populations. Herein we describe the clinicopathological clinicopathological, immunohistochemical, molecular, and ultrastructural findings of fatal human herpes simplex virus type 1 (HSV-1) infection in 13 urbanized, free-ranging, black-tufted marmosets (*Callithrix penicilatta*) in Brazil. Necrotizing meningoencephalitis, ulcerative glossitis, and necrotizing hepatitis with intranuclear viral inclusions were hallmarks of the disease. We localized HSV-1 antigens by immunohistochemistry and viral particles by transmission electron microscopy within neural cells, tongue epithelium, and hepatocytes. PCR testing confirmed HSV-1 in all cases. While nearly all prior reports of HSV-1 infection in marmosets are from captive animals, our findings highlight the risk of interspecies infectious disease transmission at the human-animal interface in anthropized environments and emphasize the importance of a One Health approach to infectious disease surveillance in these settings.

KEY WORDS: One Health, zoonoses, fatal, pathology, histopathology, immunohistochemistry, transmission electron microscopy, PCR, marmoset, synanthropic

CHAPTER 1- INFECTIOUS DISEASES OF NON-HUMAN PRIMATES AND A ONE HEALTH PERSPECTIVE

1. INTRODUCTION

Most emerging infectious diseases of human beings have originated in wildlife species, which are reservoirs of pathogens that threaten human health (Jones et al., 2008). In the past few decades, important new zoonoses have been caused by infectious pathogens that spilled over from animal to humans, including Human Immunodeficiency virus, Malaria, Leptospirosis, West Nile virus, Yellow Fever virus, Ebola virus, Nipah virus, Lassa fever virus, Hantavirus, Dengue virus, Rift Valley fever virus, Crimean-Congo hemorrhagic fever virus, Severe Acute Respiratory Syndrome Coronavirus (SARS), avian influenza viruses, Middle East respiratory syndrome coronavirus, Zika virus and more recently, the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Woolhouse et al., 2005; Jones et al., 2008; WHO, 2020). The emergence of these infectious diseases highlights the importance of creating strategies and actions to rapidly detect infectious agents in wildlife that could spread to humans.

Expansion of world populations and anthropogenic activities lead to human encroachment into wildlife habitats and favor the contact between wild animals and humans, increasing the risk of infectious disease spillover events (Chapman et al., 2009). Physiological, immunological, and genetic similarities are shared between humans and non-human primates (NHPs), allowing NHPs to be susceptible to the majority of pathogens that can jump to humans (Fuentes et al., 2012). To better understand the risk of disease spillover, research into the dynamic processes linking zoonotic disease emergence is needed, including studies on the diversity of pathogens, their ecology, and epidemiology at the human-NHP interface.

Pathology has played a critical role in discovering and advancing our knowledge of emerging and re-emerging infectious diseases in humans (Schwartz et al., 1996; Turner et al., 2012; Zaki et al., 2014). Likewise, postmortem studies of NHPs can be important from a One Health viewpoint for providing information about etiology-specific causes of death and disease surveillance. These studies also help determine NHP's role as sentinels and sources of zoonotics infections in humans and are useful in preparing strategies for the prediction and prevent of zoonotic disease transmission in the human-NHP interface. Therefore, herein we highlight the relevance of the pathological surveillance of deaths in free-ranging NPHs to identify etiologic agents of public health concern and that threaten the conservation of natural animal populations aiming to control and prevent the transmission to human populations.

2. RATIONALE

Several infectious diseases affect NHPs and have zoonotic potential. The study of these diseases is extremely important, considering the possibility of transmission to humans and the potential of these animals to become reservoirs of various zoonoses. There is limited information on the prevalence of infectious diseases in free-ranging NHPs in Brazil and their epidemiological characteristics regarding the wildlife cycle and the maintenance of infectious agents by NHPs. Furthermore, it is necessary to evaluate the impact of these infectious agents on the conservation of these species.

More studies may contribute to determination of pathological changes and characteristic patterns of lesions caused by various infectious diseases that affect NHPs, which improve the morphological diagnosis and surveillance of diseases. The Brazilian' Ministry of Health recently promoted efforts to establish an algorithm for the national diagnosis of yellow fever in NHPs, based mainly on recognizing the histomorphological patterns for recognizing zoonotic diseases in postmortem tissue samples combined with other diagnostic assays, such as immunohistochemistry and PCR. Studies of this nature can provide knowledge on the main diseases that affect NHPs populations and will be helpful to build a list of differential diagnoses leading to mortality in mortality in primates. Since etiologic agents affecting NHPs include those with zoonotic potential, these studies also expand surveillance opportunities to work to prevent and control threats to at risk human populations, which include those with zoonotic potential, thus expanding surveillance to prevent and control threats to the human populations at risk.

3. OBJECTIVES

3.1 General objectives

Perform pathological investigation to determine infectious causes of death in NHPs utilizing tissue-based diagnostic assays, including routine histopathological evaluation, special stains, immunohistochemistry, and molecular testing by RT-PCR/PCR on postmortem tissues samples at the Veterinary Pathology Laboratory at University of Brasilia, Federal District (FD), the Regional Reference Laboratory of the Brazilian Ministry of Health for Diagnosis of Yellow Fever and Epizootics in NHPs. Characterize clinical-pathological changes, and pathogenesis associated with the main disease-causing infectious agents in NHPs.

3.2 Specific objectives

i. Identify the occurrence of fatal infectious diseases of public health relevance that affects free-ranging NHP in the Federal District and surrounding areas in Brazil from 2012 to 2019.

ii. Characterize pathology and pathogenesis associated with causative fatal infectious agents of diseases in free-ranging NHPs in the study areas.

iii. Retrospective detection of infectious agents in necropsy tissues samples of free-ranging NHPs by histopathology, special stains, immunohistochemistry, and RT-PCR/PCR.

iv. Use a One Health approach to identify epidemiological factors and public health concerns or implication of infectious diseases of NHPs in study areas.

4. REVIEW OF LITERATURE

4.1 Human-non-human primate interface, One Health and conservation concerns

Most of the infectious diseases causing human pandemics are zoonoses (Jones et al., 2008). The emergence of infectious diseases depends on multiple factors of pathogen, host, and environment interaction. It is well known that parasites, viruses, bacteria, and fungi frequently have wildlife reservoirs, including NHPs, and close interactions between humans and wildlife may enable zoonotic spillover (Wolfe et al., 1998; Woolhouse et al., 2005; Jones et al., 2008). Highly pathogenic infectious agents that have originated in the sylvatic cycle in NHPs and jumped to humans include human immunodeficiency viruses, malaria, rabies, yellow fever, Monkeypox, Herpes B virus, Marburg, and Ebola viruses. Besides the risk of well-known pathogens transmission from NHPs to human beings, there is also a concern about the emergence of new infectious agents that give rise to novel pandemics (Devaux et al., 2019).

Situations driving increase in the risk of new infectious disease introduction in the human-NHP interface around the world include: hunting, meat consumption, and illegal import of meat (human contact with dead NHP carcasses), ecotourism, professionals working with NHPs in zoos, primate centers, animal facilities and anthropogenic activities including deforestation and contact between NHPs and humans in natural environments. Multiple direct and indirect routes of infection are involved in the transmission of pathogens from NHPs to humans (aerosol, direct contact, fomite, oral, and vectors) are involved in the pathogen transmission from NHPs to humans (Wolfe et al., 1998; Devaux et al, 2019).

The increase in human populations and expansion of urban areas results in encroachment into wildlife habitats and the adaptation of some natural NHPs populations to live in anthropized areas. These conditions make human-NHPs interactions and host-pathogen relationships more frequent and increase the risk of interspecies infectious diseases transmission. Ecological and behavioral characteristics of different species of NHPs in natural and anthropized environments can lead to different degrees of exposure and susceptibility to emerging infectious diseases and spillovers to humans (Chapman et al., 2005; Daszak et al., 2001; Estrada et al, 2017).

The burden of infectious diseases in Brazil is a concern for various and complex reasons, including poor health and urban infrastructure and typical cycles involved in the emergence and re-emergence of some infectious diseases (Wadman et al., 2016). Brazil and other tropical regions of the world have high biodiversity, large landmass, and population primarily living in city centers.

These areas, most in peri-urban but even in urban regions, still harbor a wildlife species richness that enables interspecies contact, circulation of pathogens, and may undergo environmental changes that drive the emergence of infectious diseases (Nava et al., 2017). The phylogenetic proximity, ecological overlap and interaction, and the high number of infectious diseases shared between humans and NHPs increase the potential for pathogens spillover (Cooper et al., 2012; Fuentes et al., 2012).

There are about 504 known NHPs species in the world geographically distributed among 90 countries, and approximately two-thirds only in Brazil, Madagascar, Indonesia, and the Democratic Republic of the Congo (Estrada et al., 2017). In Brazil, primates are the third most speciose order of mammalian species comprising 126 NHPs species, which belong to five families: Callitrichidae, Pitheciidae, Cebidae, Atelidae, and Aotidae (Quintela et al., 2020). Some species of NHPs are well-adapted species to human-altered environments, such as marmosets which are naturally found in the Brazilian Savanna and Caatinga Biome and are commonly commensal in urban and periurban areas (Duarte et al., 2011).

Health is a collaborative effort with multisectoral, and transdisciplinary approach — working at the local, regional, national, and global levels — with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment. A One Health approach is critical to strengthening health security at regional and global levels when considering the diversity of NHPs species and potential interfaces for infectious diseases transmission. More research on the transmission dynamics and mechanisms underlying these cross-species transmission events will be essential in understanding the dynamics of NHPs infectious diseases. Multidisciplinary partnerships among universities, governmental agencies, non-governmental organizations, public health surveillance services, veterinary, and medical-care communities are essential to improving our ability to detect, prevent, and control infectious threats to health and pathogen spillover. Monitoring the human-NHPs interface may reduce pandemic risk, promote global health (Wolf et al., 2020). The mass vaccination of domestic animals used for the prevention of rabies (Cleaveland et al., 2017) and the surveillance of epizootics in NHPs involved in the sylvatic cycle of Yellow Fever (de Azevedo Fernandes et al, 2021) are successful examples of this approach to prevent human exposure and control of infectious diseases.

Efforts made by governmental and research institutions using a public health approach to investigate infectious diseases in NHPs have made important contributions to our knowledge of

existing, new, and potentially emerging pathogens in NHPs. However, there are still gaps in our knowledge on NHPs infectious diseases, mainly due to incomplete sampling across primates species in different geographic regions (Cooper et al., 2013). Most studies on infectious diseases in NHPs in Brazil are reported in captive and animal facilities. Natural infections in free-ranging NHPs and their role in maintaining zoonotic transmission have still a limited knowledge. Susceptibility to infections and infection paths depends on numerous factors such as ecological, epidemiological, and behavioral dynamics (Plowright et al., 2017).

4.2 Diagnosis of Infectious diseases in non-human primates

Bacterial, viral, parasitic, and fungal zoonotic pathogens have been reported infecting free-ranging and captive NHPs in Brazil. Most of the detection methods used in studies with natural infectious diseases affecting NHPs populations in Brazil are serological or molecular assays such as PCR. Antibodies can be retained for many years after either clinical or sub-clinical infections. Therefore, serological evidence for antibodies to infectious agents does not necessarily indicate current infections (Houpikian and Raoult, 2002). PCR assays have expanded the ability to detect infectious agents, but their advantages may not outweigh them due to false-positive results related to microbial DNA contamination. These diagnostic methods are helpful in monitoring the occurrence of potential zoonotic pathogens when used alone but cannot provide the microbial disease causality, according to Koch's postulates (Antonelli and Cutler, 2016). The detection of infectious agents in tissue samples is useful for overcoming such limitations of other diagnostic methods.

Pathological investigations of infectious causes of death using tissue-based diagnostic assays, characterization of pathological changes, and detection of infectious agents within lesions by special stains, immunohistochemistry, and/or PCR provide the determination of causal chain and are valuable tools for the definition of pathogenesis and understanding of infectious diseases (Schwartz et al., 1996; Turner et al., 2012; Zaki et al., 2014). The pathological investigation is an important key for substantial advances in our knowledge and discovery of emerging and re-emerging infectious diseases. Additionally, the determination of etiology-specific causes of death and pathogenesis of zoonotic diseases is essential for selecting strategies that promote the prediction and prevention of zoonotic disease transmission. Therefore, it is critical to improve the

capabilities to detect infectious etiologies causes of death in NPHs populations with epidemic potential.

4.3 **Infectious diseases of Non-human primates in Brazil**

There have been several relevant zoonoses detected in NHPs such as rabies (Batista-Morais et al., 2000; Favoretto et al., 2001; Aguiar et al., 2011; Favoretto et al., 2006; Machado et al., 2012; Favoretto et al., 2013; Kobayashi et al., 2013) Zika, Chikungunya, Dengue (Pessôa et al., 2016), yellow fever (Azevedo Fernandes et al., 2017; Leal et al., 2016) and others as toxoplasmosis (Epiphanio et al., 2003), Chagas disease (Bahia et al., 2017), leishmaniasis (Malta et al., 2010), malaria (Figueiredo et al., 2017) and microfilariasis (Bueno et al., 2017). It is difficult to describe herein all the infectious diseases detected in NHPs in Brazil. Therefore, we will address below the agents causing fatal diseases in free-living NHPs in Brazil.

In a survey of necropsies data of NHPs conducted from 2012 to 2019 in the archives of the Veterinary Pathology Laboratory at the University of Brasilia (Regional Reference Laboratory of the Brazilian Ministry of Health for Diagnosis of Yellow Fever), the black-tufted marmoset (*Callithrix penicillata*) was the main species involved in deaths in urban and peri-urban areas in Midwestern Brazil. Although deaths in NHP prompt concerns about YF infection, case investigations have been proven useful in diagnosing other relevant infectious diseases considering the One Health approach and animal conservation view. From 1042 cases retrieved the main causes of death we identified included 20% (213) traumatic injuries, 12% (131) cases of infectious diseases (viral, bacterial, and parasitic) and 6,4% (64) electrocutions (Pereira et al., 2020). We also identified 0,5% (5) cases of neoplastic diseases. While able to provide valuable information regarding causes of death in NHPs, utilization of post-mortem specimens from necropsy tissues presents a number of technical challenges that lead to some limitations regarding the determination of the cause of death, the first of which is autolysis which makes the sample inadequate to be evaluated for a definitive diagnosis, 16 % (164) of cases were inadequate for evaluation because of autolysis. Another challenge identification of unspecific findings for determination of cause of death resulting in inconclusive results, 25% (261) of the cases were inconclusive. Other causes of death were metabolic, iatrogenic, predation or unspecific inflammation of multiple tissues. Herein we focus on the infectious causes .Studies involving infectious agents in free-living NHPs are scarce and still lack comprehension of the epidemiology of most emerging zoonotic diseases.

4.3.1 Viruses

Arboviruses

Pathogens transmitted by arthropod bite during blood meal is a concern for public health. Yellow Fever (YF) is the most relevant viral disease of free-living New World Primates (NWP) for the public health surveillance services in Latin America. YF virus belongs to the genus *Flavivirus* (family *Flaviviridae*) originated in West Africa. After its introduction, YF has become endemic in tropical regions of South America and sub-Saharan Africa. NHPs are reservoir hosts in the sylvatic cycle that is the predominant transmission cycle (Monath et al.,, 2001). The primary vectors in the sylvatic cycle are mosquitoes such as *Aedes africanus* (in Africa) and *Haemagogus* (in South America). Other mosquitos genera that can serve as vectors for the YF virus are *A. furcifer*, *A. vittatus*, *A. luteocephalus*, and *A. bromeliae* in Africa and *Sabethes chloropterus* in South America. The urban cycle of YF virus involves mainly the mosquito *Aedes aegypti* in Africa (Hanley et al., 2013). The main pathological findings of YF in NHPs include jaundice and marked midzonal hepatocellular necrosis with acidophilic, apoptotic (Councilman) bodies, accompanied by hepatic fatty change and hemorrhage (Leal et al., 2016). In NHPs, the identification of characteristic YF-associated histopathological features in addition to the viral antigen detection by IHC in post-mortem tissue samples and/or by molecular assay investigation is the recommended gold standard used for the diagnosis of YF infections (Brasil, 2017). Since the first epidemics of sylvatic YF in Brazil, efforts to strengthen the YF surveillance systems have been made primarily based on NHP epizootics surveillance (de Oliveira Figueredo et al., 2020). The Brazilian Ministry of Health initiated in 1999 the program for surveillance of YF epizootics in NHP, which became an essential tool for the control and prevention of YF (Brasil, 2017). These investments enable detection, notification, and rule-out of YF and implementation of good practices for control YF infection, such as launching the national YF vaccination campaign by the Brazilian public health authorities.

Other arboviruses infections have been sporadically detected in NHPs in Brazil, such as Zika virus (Moreira et al., 2018; Terzian et al., 2018; Favoreto et al., 2019); Mayaro virus, Cacipacoré virus, virus, and Oropouche virus (Batista et al., 2013), Chikungunya virus (Moreira-Soto et al., 2018) and hepatitis A (Svoboda 2016., et al). Seroepidemiological surveys have also detected but do not specify other flaviviruses infections in free-ranging NHPs in Brazil (Catenacci

et al., 2018). These studies highlight the relevance of NHPs as potential reservoirs for zoonotic diseases. Despite the limited knowledge and evidence of other arboviruses infections than YF in NHPs without clinical signs or fatal disease, further studies to evaluate the role of these animals in the sylvatic cycle and as hosts are needed and of great relevance to Public Health (Moreira-Soto et al., 2018).

Rabies

Rabies is a zoonotic disease caused by the rabies virus of the genus Lyssavirus belonging to the family Rhabdodovidae. Two cycles are involved in the maintenance and transmission of the disease; the urban cycle, which has the dog as the main reservoir and transmitter; and sylvatic rabies, which has a variety of wildlife species as reservoirs and/or transmitters (Garg, 2014). Rabies is responsible for around 59,000 fatal human encephalitides annually, most of than occurring in Africa and Asia (WHO, 2013). In Brazil, various domestic and wildlife species act as receivers and are responsible for maintaining and transmitting rabies virus in the urban and sylvatic cycle, respectively (Meske et al., 2021).

There are few descriptions of fatal natural rabies virus infection in NHPs (Favoretto et al., 2013). In a study in Ceara State, Northeastern Brazil, eight cases of fatal human rabies were related to exposure and transmission by white-tufted marmosets (*Callithrix jacchus*) (Favoretto et al., 2001). From 2002 to 2012, 52 cases of rabies in NHPs were confirmed as part of the National Program for Rabies Control and Prophylaxis. Most of the cases (n=51) occurred in marmosets from Ceará and a single case in a Capuchin monkey from Mato Grosso State (Rocha et al. 2017). A seroepidemiological study identified antibodies against rabies in 11% of free-ranging tufted capuchin monkeys (*Sapajus apella*) in Sao Paulo State, Southeastern Brazil (Machado et al. 2012). These studies highlight that marmosets are involved in the maintenance and transmission of rabies in Brazil. The proximity of marmosets' habitats to inhabited areas and free-ranging animals living in urban areas may contribute to the emergence of the disease (Favoretto et al., 2001). A-One Health approach for the surveillance, conservation of natural environments, and public health strategies such as mass vaccination can be used to prevent cases of rabies in human populations (Cleaveland et al., 2017).

Clinical signs of natural rabies infection in NHPs are not well known. Infection was reported to cause furious and paralytic forms of rabies, characterized by clinical manifestations

such as self-mutilation, irritability, and paralysis of pharyngeal and pelvic muscles (Fiennes, 1972). Post-mortem diagnosis is based on typical histopathological findings of nonsuppurative meningoencephalitis with eosinophilic intracytoplasmic inclusions within nerve bodies (Negri-bodies). Diagnosis confirmation can be made by fluorescent antibody test or immunohistochemical assay in brain tissues samples, preferably the brain stem and cerebellum, using a rabies-specific antibody. Virus isolation and molecular biologic identification can also be additionally used for the diagnosis (Garg, 2014).

Herpesviruses

Herpesviruses infections cause latent or subclinical infections in their natural hosts and have been related to cause acute fatal diseases in non-natural hosts. *Macacine herpesvirus* 1 or B-virus and Herpes simplex virus (*Human herpesvirus* 1) are the most important alphaherpesviruses regarding human and animal infections due to zoonotic potential to lead to severe fatal disease in the accidental host. Herpes Simplex Virus 1 (HSV-1) is endemic in human populations (natural host) and usually has a benign presentation. Atypical morbidity can occur in neonates and severely immunocompromised patients causing severe mucocutaneous lesions and rarely a disseminated disease with hepatitis and encephalitis (WHO, 2020).

The HSV-1 infection occurs through the viral epithelial invasion by direct or indirect contact with mucocutaneous lesions or transmitted by viral shedding from an asymptomatic host (Gregory et al., 2008). Viral shedding occurs essentially through bodily secretions (e.g. aerosol, respiratory droplets, saliva, or other contaminated excretions) from infected individuals (Mätz-Rensing et al., 2003; Lefaux et al., 2004; Tischer and Osterrieder, 2010). Experimental HSV-1 infection in Rhesus macaques demonstrated ocular, nasopharyngeal, oral, fecal and urine virus shedding from three to ten days post-infection (Fan et al., 2017).

Most epizootics of HSV-1 in NHPs are initiated by man-to-animal interaction and transmission (Mätz-Rensing et al., 2003). Natural fatal HSV-1 infections crossing interspecies barriers have been reported in situations of close contact between these animals and humans that increase the risk of transmission of pathogens such as in pet New World Primates (NWPs) conditions, when kept in household, captive at zoos, or in animal facilities of biomedical research centers (Juan-Sallés et al., 1997; Mätz-Rensing et al., 2003; Schrenzel et al., 2003; Lefaux et al., 2004, Hatt et al., 2004; Costa et al, 2011; Imura et al., 2014; Casagrande et al., 2014; Barnes et al.,

2016, Edwards et al., 2018; Huemer et al., 2020). On the other hand, HSV-1 infections are rarely observed in free-ranging NHPs, with some isolated outbreaks in anthropogenic environments (Bruno et al., 1997; Longa et al., 2008).

Herpes simplex infections have distinct clinical presentations between NWP, old-world primates, and human beings. Latent or subclinical infections predominate in the natural hosts, and severe disease or death is the general rule forthe interspecies HSV-1 transmission (see Table 3, Chapter 3). High morbidity and mortality have been reported in the HSV-1 infection of NWP (Bruno et al, 1997; Juan-Sallés et al., 1997; Schrenzel et al., 2003; Lefaux et al., 2004, Hatt et al., 2004; Longa et al., 2008; Imura et al., 2014; Barnes et al., 2016, Edwards et al., 2018; Huemer et al., 2020), ranging from more than 70% to 100% of mortality (Mätz-Rensing et al., 2003, Costa et al., 2011; Casagrande et al., 2014). A animal-to-animal HSV-1 spread possibly increases morbidity and mortality within family groups and captive NHPs (Lefaux et al., 2004). In contrast, fatal cases are rarely reported in old-world monkeys infections that appear to be self-limiting such as in human beings (Gilardi et al., 2014; Landolfi et al., 2005; Kik et al., 2005; Landolfi et al., 2005).

Clinical manifestation of HSV-1 infection in NWP includes mucocutaneous facial and oral erosion/ulcerations and neurological signs (Juan-Sallés et al., 1997; Mätz-Rensing et al., 2003; Schrenzel et al., 2003; Lefaux et al., 2004, Hatt et al., 2004; Costa et al, 2011; Imura et al., 2014; Casagrande et al., 2014; Barnes et al., 2016, Edwards et al., 2018; Huemer et al., 2020). In marmosets, sudden death within 3 days after the first onset of symptoms has also been reported and presented the fulminant course of the HSV-1 infections (Mätz-Rensing et al., 2003). Hypersalivation and oral bleeding have also been reported in marmosets with acute HSV-1 infections (Mätz-Rensing et al., 2003; Hatt et al., 2004; Costa et al., 2011; Casagrande et al., 2014).

Pathological findings include vesicles and ulcers in the mouth, tongue and genital areas, and animals with longer course illness develop necrotizing meningoencephalitis. Histopathologic changes consist of severe vesicular and ulcerative lesions in the squamous epithelia of the mucous membranes and the tongue with ballooning degeneration and acantholysis. Chronic infections lead to nonsuppurative meningoencephalitis. Characteristic multinucleated syncytia and intranuclear, eosinophilic inclusion bodies are associated with these lesions (Hatt et al., 2004; Mätz-Rensing et al., 2003). Identification of typical pathological findings together with antigens detection by immunohistochemistry, ultrastructural viral detection, and confirmation with molecular analysis is usually used to diagnose the disease (Mätz-Rensing et al., 2003).

Animal models have shown that primary HSV-1 infection takes place through the skin or oral mucosa and is usually followed by a latent stage in sensory neurons and further reaches the brain through the trigeminal nerve or olfactory bulb to cause lethal encephalitis (Sehl et al., 2020). HSV-1 replication seems to trigger cytopathic effects such as programmed cell death and necrosis (Wang et al., 2014). The pathogenesis of epithelial and brain lesions also includes a severe immune and inflammatory-associated response (Zimmermann et al., 2017). The central nervous system inflammatory infiltrate composed of macrophages, CD4+ and CD8+ T lymphocytes, and NK cells and is likely triggered by the host immune response against the HSV-1 (Kastrukoff et al., 2010).

Macacine herpesvirus 1 (B-virus) is transmitted from macaques to humans and is the most important zoonotic herpesvirus for public health; human infections are related to captive monkeys exposure in biomedical research facilities. Nevertheless, close contact with synanthropic macaques could be a possible risk to human health (Tischer and Osterrieder, 2010). In mature adult wild macaques and captive populations, the prevalence can range from 45% to almost 90% Analogous to HSV-1 infection in humans, B-virus is asymptomatic or mild in natural hosts (macaques), which develop viral latency in trigeminal and lumbosacral ganglia and shedding in oral and genital secretions. In contrast, human beings develop severe and fatal meningoencephalitis (Engel et al., 2002). Histopathological findings consist of vesicles and epithelium ulceration with ballooning degeneration, multinucleated syncytial giant cells formation, and typical eosinophilic intranuclear viral inclusion bodies on the edge of areas of necrosis. Fatal infection is rare and can occur in immunosuppressed animals and present as a disseminated disease characterized by necrotizing inflammation liver, lung, and brain (Thompson et al., 2000). Fatal Herpes B virus infections have not been identified in free-living NHPs in Brazil.

4.3.2 Bacteria

Leptospirosis

Leptospirosis remains a public health concern and a worldwide zoonotic emerging disease. Leptospira species have been detected in a wide range of wild and domestic mammalian reservoirs. Transmission to humans occurs by direct contact with reservoir animals or indirect exposure to the environment, water, and moist soil contaminated with pathogenic *Leptospira* (Adler et al, 2010). Naturally acquired fatal leptospirosis is uncommon in non-human primates (NHPs) and has been reported only in animals in captive conditions (see Table 1, Chapter 2) (Fear et al., 1968; Shive et

al., 1969; Perolat et al., 1992; Reid et al., 1993; Scarcelli et al., 2003; Baitchman et al., 2006; Szonyi et al., 2011; Gonzalez-Astudillo et al., 2015). In NHPs, serological surveys indicate that naturally acquired leptospirosis can be a subclinical disease and suggest that this animal could serve as an asymptomatic source of infection (Pinna et al., 2012). Symptomatic infections and death have been reported in captive animals in zoos, rehabilitation, and research centers (Shive et al., 1969; Perolat et al., 1992; Reid et al., 1993; Scarcelli et al., 2003; Baitchman et al., 2006; Szonyi et al., 2011). Experimental studies of leptospirosis in NHPs have been conducted as a model for the disease in humans (Pereira et al., 2005).

Jaundice, unspecific clinical signs (weight loss, lethargy, vomiting, and diarrhea), and acute death with no apparent clinical signs are common clinical findings in fatal cases in marmosets naturally infected with *Leptospira* spp. Other clinical signs reported included hemorrhagic syndrome, respiratory distress, seizures, and abortion. An outbreak was reported causing a high rate of abortion in a colony of Baboons (*Papio* sp) , and serology indicated *Leptospira ballum* as the causative agent (Fear et al., 1968).

Gross lesions of leptospirosis include icterus of mucous membranes, subcutaneous tissues, and viscera; pulmonary hemorrhage and edema; visceral hemorrhage, petechia, and ecchymosis; hepatomegaly; nephromegaly; increased friability of liver and kidney, hematemesis, epistaxis, purpura, melena and free blood in thorax and abdomen. Renal lesions include interstitial nephritis, congestion, vacuolar degeneration, and necrosis of renal tubular epithelium, exudative glomerulopathy and cast formation with hemorrhage in tubular lumens. The lung can show hemorrhagic pneumonitis and edema, and liver injury include hepatocellular dissociation, hepatic necrosis, and periportal hepatitis (Fear et al., 1968; Shive et al., 1969; Perolat et al., 1992; Reid et al., 1993; Scarcelli et al., 2003; Baitchman et al., 2006; Szonyi et al., 2011; Gonzalez-Astudillo et al., 2015).

Experimental leptospirosis infections in NHPs demonstrated variable clinical forms and outcomes. Mild illness with transient immunity and recovery was observed in patas (*Cercopithecus patas*), rhesus (*Macaca mulatta*), Cebus (*Cebus* sp.), and vervet (*Cercopithecus aethiops*) monkeys, in contrast to the severe illness characterized by jaundice and fatal outcome in squirrel monkeys (*Saimiri sciureus*) (Minette et al., 1968). Marmosets (*Callithrix jacchus*) were susceptible to experimental infection by *Leptospira interrogans* serovar Copenhageni isolated from a human fatal case of the pulmonary form of leptospirosis. Marmosets also develop a severe pulmonary

form that resembles the disease in humans. Gross necropsy lesions included lungs with pleural surface hemorrhages. Histological evaluation showed severe intra-alveolar hemorrhages with interstitial pneumonitis, acute tubular necrosis, severe tubulointerstitial nephritis, and multifocal hepatic necrosis with occasional Councilman bodies (Pereira, 2005). On the other hand, Grivet monkeys infected by *Leptospira interrogans* serovar hardjo showed no clinical signs or lesions (Palmer et al., 1987).

Different types of laboratory tests can be used for definitive diagnosis of leptospirosis: isolation of *Leptospira* by culture methods; serological diagnosis by microscopic agglutination test (MAT); DNA detection by PCR; indirect hemagglutination assay (IHA); enzyme-linked immunosorbent assays (ELISA). MAT has been usually used for the diagnosis because other tests can be complicated by proper material availability expertise requirements, and slow results (Levett, 2001). Leptospira antigens can be detected by immunohistochemical assay on formalin-fixed tissues samples and are considered a valuable tool for post-mortem diagnosis (Trevejo et al, 1995; Zaki et al., 1996). Seroprevalences of asymptomatic Leptospira infections have been reported in captive NHPs (Pinna et al., 2012). In captive Capuchin monkeys (*Sapajus apella*), 71% of animals kept in a wildlife rehabilitation center showed clinical signs of leptospirosis, 27% died, and two animals were asymptomatic carriers (Szonyi et al., 2011).

The probable source of infection for natural leptospirosis in NHPs is contaminated water, food, or animal facilities with the presence of infected synanthropic rodents (Fear et al., 1968; Shive et al., 1969; Perolat et al., 1992; Reid et al., 1993; Baitchman et al., 2006; Szony et al., 2011; González et al., 2015). Identification of serovars involved in epizootics of leptospirosis is important to investigate sources of infection related to particular carrier hosts for specific serovars (Marini et al, 2018).

Actinomyces

The *Actinomyces* spp. genus comprises gram-positive, anaerobic, filamentous bacteria that promote non-contagious, chronic, slowly progressive, and pyogranulomatous diseases. Pathogenic *Actinomyces* spp. are commensal bacteria that inhabit the mucosa of the digestive tract of mammals and are considered opportunistic pathogens requiring previous tissue damage, inhalation of contaminated aerosols, or immunosuppression conditions for their systemic dissemination (Valour et al., 2014). There is one report of fatal pulmonary actinomycosis in a free-living black-tufted

marmoset. Grossly multiple nodules with purulent content were reported, and microscopically, infection was characterized by colonies of filamentous Gram-positive and modified Ziehl–Neelsen-negative bacilli associated with necrosis and inflammatory reaction composed of numerous epithelioid macrophages, Langerhans-type giant cells, intact and degenerated neutrophils, and *Splendori-Hoepli* phenomenon. PCR assay confirmed *Actinomyces* sp. infection (Sousa et al., 2019).

Other Bacteria

Regarding other bacterial infections, enterobacterial pathogens, frequently found in human microbiota, have been detected in free-living NHPs from anthropized areas in Brazil, suggesting that it may have crossed from humans to NHPs (Zaniolo et al., 2018). *Borrelia burgdorferi* infection was detected in free-living golden-headed lion tamarins (*Leontopithecus chrysomelas*) in Rio de Janeiro by PCR, suggesting a role NHPs in the transmission of this pathogen to other animals or human beings (Santos et al., 2018). Molecular identification of *Mycoplasma* spp. in captive and free-living NHPs in Brazil (Bonato et al., 2015; Cubilla et al., 2017; de Melo et al., 2019). Fatal *Mycobacterium tuberculosis* infections were reported in NHPs from Brazil, but only in captive animals (Rocha et al., 2011; Ehlers et al., 2020)

4.3.3 Protozoan

Toxoplamosis

Toxoplasma gondii is an intracellular coccidian protozoan with high zoonotic potential that infects non-human primates worldwide (Minervino et al., 2017). The life cycle of toxoplasmosis has the felids as definitive hosts, which shed stable and environmentally resistant oocysts in the feces (Santos et al., 2018). Environmental contamination facilitates horizontal transmission through water, fruits, and vegetables, and consumption of raw or undercooked meats is responsible for the contamination of intermediate hosts in the postnatal form (Minervino et al 2017; Epiphanio et al., 2003).

Several cases of toxoplasmosis have been reported in captive New and Old-World Primates (Kamau et al., 2019; Nishimura et al., 2019; New World Primates are considered more susceptible to toxoplasmosis, presenting the disease in non-seasonal outbreaks leading to the death of several

individuals without or with specific clinical signs (Nishimura et al., 2019). Environmental fragmentation, anthropogenic actions in their habitats, and the of these primates to urban areas are likely associated with an increase in the vulnerability to the infection (Yan et al., 2016). Most affected NWPs by toxoplasmosis have arboreal habits, which limits contacts with felids and thus *T. gondii*. This particularity could explain the susceptibility of these animals to the disease due to not having developed an efficient evolutionary immune response to the parasite due to lack of contact with felids and *T. gondii* oocysts. These facts suggest that domestic cats in urban environments allow the contamination of water or food by oocysts in addition to the possible ingestion of infected rats by monkeys, which increases the risk of infection (Carme et al., 2009).

Limited data is available on the occurrence of *T. gondii* in free-ranging NPHs in Brazil. Pathological, serological, and molecular evidence of *T. gondii* infection were reported in different NHPs species (Molina et al., 2014; Santos et al., 2018). In captive animals, the disease is characterized histopathologically by multifocal random necrotizing hepatitis, lymphadenitis, interstitial pneumonia, and necrotizing splenitis with *Toxoplasma gondii* free tachyzoites or cysts containing bradyzoites. Detection of the protozoan organism in tissues can be performed by ultrastructural analysis and immunohistochemical assay for *T. gondii* antigens (Epiphanio et al., 2003).

Toxoplasmosis is an important public health problem worldwide. Free-living NHPs inhabit intensely urbanized areas and are closely related to humans. The occurrence of toxoplasmosis and the relevance of NHPs in the transmission chain must be investigated to formulate prevention and control strategies.

Other protozoans

Other protozoan infections have been identified in captive and free-living NHPs in Brazil, including *Leishmania* sp., *Trypanosoma* sp. and *Plasmodium* sp. Experimental studies evidenced the susceptibility of NHPs to *Leishmania* sp infection (Silveira et al., 1990). Most reports of *Leishmania* sp infection in captive and free-ranging NPHs are asymptomatic and detected by serology and molecular assays NHPs (Malta et al., 2010; Lima et al., 2012; Bueno, 2012; Bueno et al., 2017; Paiz et al., 2019). A fatal case of *Leishmania chagasi* infection was reported in a captive black-fronted titi (*Callicebus nigrifrons*). The animal showed histiocytic hepatitis, lymph-plasmo-

histiocytic interstitial nephritis, pulmonary hemorrhage and edema, and intralesional amastigotes forms were detected histologically by immunohistochemistry, and PCR detection (Malta et al., 2010). The epidemiology of *Leishmania* sp. infection in NHPs is limited, one study suggests that captive NHPs may play a role in the leishmaniasis cycle, and they are considered sentinels to the disease (Rodrigues de Oliveira et al., 2019).

Regarding *Trypanosoma* sp., natural infections have been detected by molecular and serological studies in free-ranging NHPs in Brazil (Bueno et al., 2017; Bahia et al., 2017; Lisboa et al., 2000). One study demonstrated that free-ranging golden lion tamarins (*Leontopithecus rosalia*) with *T. cruzi* positive serology presented clinical, biochemical, and electrocardiographic alterations (Monteiro et al, 2006). Fatal Chagas disease was reported in captive Baboons in the United States associated with myocarditis and visualization of amastigotes in heart tissues. *T. cruzi* infection was confirmed by blood culture, immunohistochemistry, and PCR (Williams et al., 2009; Andrade et al., 2009).

Malaria is an acute febrile illness caused by *Plasmodium* sp. originated in sylvatic environments from NHPs and infects humans and NHPs (Prugnolle et al. 2011). In NHPs, malaria is a subclinical, non-fatal disease associated with anemia and parasitemia in some animals (Bueno et al., 2013). *Plasmodium* sp. infections have been identified in free-living NHPs in Brazil, and surveillance of malaria in NPHs is relevant for Public Health since they are possible natural reservoirs (Alvarenga et al., 2015).

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CHAPTER 2 - Pathology and One Health implications of fatal *Leptospira interrogans* infection in an urbanized, free-ranging, black-tufted marmoset (*Callithrix penicillata*) in Brazil*

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CHAPTER 3- Fatal human herpes simplex virus type 1 infection: a deadly threat for free-ranging black-tufted marmosets living in anthropized environments.*

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