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Infectious agents and reproductive disorders in non-human primates used as biomodels in animal experimentation

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Abstract. Reproductive disorders in non-human primates can be caused by a range of factors, in particular by infectious diseases. The literature review presented here aimed to identify the principal pathogens that can cause reproductive disorders in nonhuman primates, in particular, in the experimental models used for biomedical research. Although it is still largely unclear to what extent the pathogens as *Coxiella burnetii*, *Brucella* spp., *Toxoplasma gondii*, and *Mycoplasma* spp. can cause similar reproductive disorders in nonhuman primates, as observed in the human population and other animal group, we concluded that it would be strongly recommended to test for infection by these infectious agents all captive nonhuman primates with a history of reproductive disorders.

Keywords: Primates, reproductive disorders, bacteria, protozoa

Agentes infecciosos e desordens reprodutivas em primatas não humanos usados como biomodelos na experimentação animal

Resumo. Os distúrbios reprodutivos em primatas não humanos podem estar associados com uma série de fatores, em particular com doenças infecciosas. A revisão de literatura aqui apresentadas teve como objetivo identificar patógenos que podem causar distúrbios reprodutivos em primatas não humanos, em particular, nos modelos experimentais usados para pesquisas biomédicas. Embora não esteja totalmente claro até que ponto patógenos como *Coxiella burnetii*, *Brucella* spp., *Toxoplasma gondii* e *Mycoplasma* spp. possam causar distúrbios reprodutivos semelhantes em primatas não humanos, como observado na população humana e de outros grupos de animais, concluímos que seria altamente recomendável testar para infecção por estes agentes infecciosos todos os primatas não humanos mantidos em cativeiro com histórico de distúrbios reprodutivos.

Palavras-chave: Primatas, distúrbios reprodutivos, bactérias, protozoários

Introduction

Non-human primates are closely-related to humans, and present a number of behavioral, anatomical, and physiological similarities. New World Monkeys (NWMs), infraorder Platyrrhini, can be distinguished from Old World Monkeys (OWMs), infraorder Catarrhini, primarily by their more widely-spaced nostrils. The NWMs are generally smaller than OWMs, have less opposable thumbs, lack ischial callosities and cheek pouches, and have three, rather than two premolars in each tooth row (Rylands & Mittermeier, 2009). All NWMs are also strictly arboreal, and are thus restricted to forested habitats in Central and South America (Magalhães, 2012).

Given their genetic similarities with humans, these primates are widely-used as biomodels for animal experimentation, in particular vaccine validation tests. Some platyrrhine species are more suitable for specific types of tests, given their response to certain infectious agents. Marmosets (*Callithrix*), for example, are widely used to test leishmaniasis, while capuchins (*Cebus* and *Sapajus*) are included frequently in research in neurosciences, dentistry, and in particular, the behavioral sciences (Verderane & Izar, 2019). Squirrel monkeys (*Saimiri*) are a model for research on malaria (drugs and vaccines), and metabolic and cardiovascular diseases (Otoch et al., 2012). Recent studies have also shown that nonhuman primates provide an excellent model for the study of a number of different strains of human tuberculosis, *Mycobacterium tuberculosis* (Peña & Ho, 2016; Scanga & Flynn, 2014).

A number of factors, including both infectious and non-infectious agents, are associated with reproductive disorders in primates. Factors such as reproductive age, birth interval, primiparity, obesity, genetic traits (inbreeding), management stress, and a lack of well-being can influence the frequency of miscarriage, although infections with microorganisms are by far the most important cause of these disorders (Souza, 2010). The infectious agents that be associated with reproductive disorders in non-human primates are *Brucella* sp., *Coxiella burnetii*, *Mycoplasma* spp., and *Toxoplasma gondii*.

Material and method

The following databases were used to search for articles in English and Portuguese language from January 1979 to December 2019: PubMed, Google Scholar e Scielo. The following search terms were used: animal experimentation, non-human primate, infectious agents and reproductive disorders. Abstracts were reviewed and relevant articles that met the inclusion criteria – only articles on infectious agents in non-human primate in the context of animal experimentation - were selected to review in full.

Results and discussion

In total, 39 studies were identified and selected to review in full. Thus, due to the reduced number of studies on reproductive disorders caused by infectious agents in non-human primates as experimental animals, the results of selected articles with brief considerations about the infectious agent are presented below.

Brucella spp.

Non-human primates are used as biomodels for testing *Brucella* in a number of different countries. Russell-Lodrigue et al. (2018) infected Rhesus macaques (*Macaca mulata*) with *Brucella melitensis* by the inhalation of small particles. This is the first report of the experimental infection of non-human primates with *Brucella*, which spread to a number of different tissues. Mense et al. (2004) conducted a similar study in Rhesus macaques, which were infected experimentally with *B. melitensis*, and presented pathologic alterations similar to those observed in human brucellosis. Yingst et al. (2010) also confirmed that the Rhesus macaque is a good model of human brucellosis in an experimental study with *B. suis*, finding the bacteria or their DNA in samples extracted from different tissues, including this of the liver, spleen, and bone marrow (Yingst et al., 2010).

The Gram-negative bacteria of the genus *Brucella* are facultative intracellular microorganisms responsible for human brucellosis, a zoonosis transmitted through aerosol inhalation when in direct or indirect contact with infected animals, mainly goats, sheep, and cattle with reproductive disorders (abortion, and premature births), or their secretions. These bacteria are considered to be a potential bioterrorism threat by the United States Center for Disease Control and Prevention. *B. melitensis*, *Brucella abortus*, *Brucella suis*, and *Brucella canis* are the species most often responsible for the spread of disease in human populations. Each of these species tends to be associated with a certain type of domestic animal, that is, *B. abortus* is found more frequently in cattle, *B. mellitensis* in sheep and goats, *B. suis* in pigs, and *B. canis* in dogs (Khan et al., 2019).

Brucella is an important group of infectious agents associated with reproductive disorders in animals, in particular cattle and other small ruminants raised in areas that lack effective public health and veterinary care programs. Transmission may occur through the ingestion of raw or unpasteurized dairy products or contaminated milk, the contact of mucosas and skin abrasions with contaminated material,

and the inhalation of aerosols or dust containing bacterial particles. Schlabritz-Loutsevitch et al. (2009) identified a new type ofnaturally-acquired *Brucella* in stillborn baboon (*Papio hamadryas*) fetuses using a Polymerase Chain Reaction (PCR) technique. Baboons in the study colony had been serum-reactive 45 years previously (Schlabritz-Loutsevitch et al., 2009).

Toxoplasma gondii

Little is known of *Toxoplama gondii* infection in captive primates. In China, Li et al. (2010) rook serum samples from cynomolgus monkeys (*Macaca fascicularis*) kept in captivity at the primatology centers in Guangxi Zhuang and Guangdong for a modified agglutination test, which showed that five (1.4%) animals had antibodies for *T. gondii*. In a similar study covering the period between 2002 and 2018, Cano-Terriza et al. (2019) identified a high seroprevalence (45.5%) in 33 species of nonhuman primates from eight zoos in Spain. In this study, the highest prevalence was recorded in adult female great apes (family Hominidae). Additional serum samples were also analyzed prospectively in this study, and in some cases, the samples of animals that had tested positive presented a significant, gradual decline in their antibody titers, while other animals that had previously tested negative subsequently presented positive samples, as observed in *Pan troglodytes*. No evidence of clinical signs of infection by *T. gondii* was found in any of the non-human primates, however. In fact, although higher rates of *T gondii* infection were recorded in adult female sin this study, which implies an increased risk of congenital toxoplasmosis, reproductive disorders such as miscarriage, stillbirth or congenital disorders could not be linked systematically to *T. gondii* infection (Cano-Terriza et al., 2019).

Data on *T. gondii* infections in nonhuman primates in Brazil are scarce, although Minervino et al., (2017) reported a seroprevalence of 49.2% in monkeys kept at the National Primate Center in Pará state, including platyrrhines and the catarrhine vervet monkey (*Cercopithecus aethiops*). This study was based on the use of parasites fixed in formalin as the antigen for a modified agglutination assay. In the state of Mato Grosso do Sul, Leite et al. (2008) detected anti-*T. gondii* antibodies in 28.7% of the captive tufted capuchins (*Sapajus apella*) keptat the Wild Animal Rehabilitation Center in Campo Grande, using indirect immunofluorescence assay, and in 30.8% of these animals, when tested using modified agglutination. This high rate of infection was linked to the ingestion of *T. gondii* oocysts contained in the captive diet, in particular, raw meat, and the predation of small animals, such as birds and rats, by these monkeys.

Santos et al. (2018) recorded a fatal case of acute systemic toxoplasmosis in a wild adult female southern muriqui (*Brachyteles arachnoides*) from the Brazilian state of São Paulo. This animal had a history of eating raw meat and contact with cats in the vicinity of the forest it inhabited. The necropsy and immunohistochemical analyses indicated acute hemorrhagic fibrin bronchopneumonia. The PCR testing returned positive results for the lung, liver, spleen, heart, skeletal muscle, and whole blood, and identified a new genotype not been previously described in primates (Santos et al., 2018).

Toxoplasma gondii has been reported in a number of different primate species in captivity, mainly in animals kept in zoos. In São Paulo, Brazil, Epiphanio et al. (2000) identified *T. gondii* through immunohistochemical analyses of a number of platyrrhine primates that had died in captivity, possibly as a result of feeding on *Tenebrio* larvae or crickets, or through the dispersal of oocysts in the environment. *Toxoplasma gondii* is the coccid protozoan that causes toxoplasmosis, which is a zoonosis of considerable importance in both human and animal health. The principal hosts of this protozoan are felines. Human toxoplasmosis is transmitted typically through the ingestion of cysts in animal tissue or contact with oocysts in the environment. Vertical transmission of tachyzoites through the placenta can occur in mothers infected with *T gondii*, provoking miscarriages, stillbirths, and congenital toxoplasmosis. Up to now, no studies have confirmed that this protozoan causes reproductive disorders in nonhuman primates, but this does seem likely, given their genetic similarities with humans (Oliveira et al., 2019; Salvo & Chomel, 2020).

Mycoplasma spp.

Møller et al. (1978) described an experiment in which *Mycoplasma hominis* was isolated from a human patient with acute salpingitis and inoculated into the uterine tubes of female vervet monkeys (*Cercopithecus aethiops*). This study obtained promising results in the tests for inflammation in the

female genital organ. Novy et al. (2009) also studied *M. hominis*, extracted postpartum from a human placenta in a patient that had developed a fever. This isolate was inoculated in pregnant female Rhesus macaques (*Macaca mulatta*) and the fetus samples were PCR positive for *M hominis*, a similar result identified by Møller et al. (1978). *Mycoplasma hominis* is a major cause of fetal inflammation, and also causes premature births and non-fetal pneumonia in nonhuman primates, and these findings provide important insights for the prophylaxis or treatment of these disorders, and their eventual prevention.

A number of new species have been described in naturally-infected nonhuman primates, including *Candidatus Mycoplasma aoti*, detected in the owl monkey (*Aotus trivirgatus*) and *Candidatus* Mycoplasma haemomacaque, which was recorded in *Macaca fascicularis* in the United States (Barker et al., 2011; Neimark et al., 2001). In addition, *Candidatus Mycoplasma haemominutum* was found in *Saimiri sciureus* in Guyana (Neimark et al., 2002) and *Candidatus* Mycoplasma haemomacaque was detected in *Macaca fuscata* in Japan (Sashida et al., 2013).

With advances in molecular techniques, PCR has been used increasingly to identify *M. fermentans* in biological samples, allowing this bacterium to be associated with systemic infections, as seen in non-human primates (Lo et al., 1993; Wang et al., 1992).

In the Brazilian state of Santa Catarina, Santos et al. (2013) detected hemotropic *Mycoplasma* in free-ranging black howler monkeys (*Alouatta caraya*) using molecular techniques. More recently, Melo et al. (2019) detected the presence of the DNA of *Mycoplasma* sp. in the serum of captive howlers (*Alouatta* spp.). These samples were assigned to two phylogenetic groups –*Mycoplasma haemofelis* and *Mycoplasma suis* – which should be taken into consideration during any further epidemiological investigation.

The genus *Mycoplasma* encompasses a group of uncultivable intracellular pleomorphic Gram negative bacteria that lack a cell wall, have a small genome, and an ample diversity of species and animal hosts (Groebel et al., 2009). Although *Mycoplasma pneumoniae* and *Mycoplasma genitalium* are associated with human diseases, the majority of *Mycoplasma* species have been described in cattle, goats, and sheep, in which they cause hemolytic anemia after attaching themselves to the surface of the erythrocytes. Most *Mycoplasma* species are highly contagious and a number of species have already been described in nonhuman primates, primarily in animal experimentation studies. Since the 1970s, in fact, non-human primates have been used as the principal animal biomodel for experimental research into reproductive disorders in women in many regions around the world (Messick, 2004; Møller et al., 1978; Novy et al., 2009).

Coxiella burnetii

Studies of *Coxiella burnetii* involving non-human primates are related primarily to the development of vaccines, with primates being considered excellent biomodel for this research. The cynomolgus monkey (*Macaca fascicularis*) is the most widely-used primate model for research on *C. burnetiid* vaccines, and is considered to be the most appropriate biomodel, considering the similarity of its clinical signs and pathological changes to those observed in humans, such as fever and pneumonia, as well as its capacity to maintain antibodies from both phases of the disease circulating for up to months (Gonder et al., 1979; Gregory et al., 2019; Kishimoto et al., 1981; Metters et al., 2019; Waag et al., 1999, 2002). Up to now, however, the publications referring to *C. burnetii* in non-human primates have been restricted to experimental research on vaccines, and no studies have linked *C. burnetii* specifically to a reproductive disorder in these primates.

One of the agents that are most associated with reproductive disorders in animals is the proteobacterium *C. burnetii*, an intracellular Gram-negative spore-forming bacterium that is known to infect an ample range of animals, including humans. This short and pleomorphic rod bacterium, which is stained using the Gimenez method, is causative agent of Q fever in humans and coxiellosis in animals. This bacterium is transmitted from animal to animal via the inhalation of dust or droplets containing spore-like particles of infected feces, urine, milk, and placentas or other uterine tissue. Ticks may also transmit *C. burnetii* to a number of wild and domestic animal species, but not to humans. A single *C. burnetii* spore-like particle can cause an infection.

Conclusion

Given their considerable genetic similarities with humans, non-human primates are important biomodels for the experimental infection of a number of infectious agents. In particular, infection by *Brucella* spp., *T gondii*, *C. burnetii*, and *Mycoplasma* spp. should be considered in non-human primates that have a history of miscarriage, stillbirth or other reproductive disorders, in particular those kept in captivity, although it is still largely unclear to what extent these pathogens cause similar reproductive disorders in human and nonhuman primates. Clearly, more systematic studies are needed to establish causal relationships between the pathogens and their potential disorders, but in the meantime, it would be strongly recommended to test all captive nonhuman primates with a history of reproductive disorders for infection by these infectious agents.

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