Chapter 5

Experimental Models of Ocular Toxoplasmosis

Aléx Martins Nasaré and Roberto Carlos Tedesco

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67947

Abstract

First described in *Ctenodactylus gundi* and simultaneously in rabbit, *Toxoplasma gondii*, an etiological agent of toxoplasmosis, affects different species of vertebrates and invertebrates, presenting different manifestations depending on the host. Ocular toxoplasmosis is one of the mean manifestations of toxoplasmosis in humans, affecting 2% of infected individuals in Europe and North America. Otherwise many aspects of ocular toxoplasmosis still await answer. One of the major factors limiting this process is the difficulty to obtain human samples, doing necessary the use of experimental models. By the way, animal models do not express reality of human disease. The present study defines a compilation of report cases and results that supports the choice of an ideal experimental animal model of ocular toxoplasmosis. Actual literature bears new researches contributing in the choice of a specific experimental animal model. Moreover, the choice must consider behavior, period of life, and maintenance in captivity and ocular toxoplasmosis manifestation. Previous studies contribute for a best-chosen experimental animal model, by the way fragmented information makes difficult to compare mostly animal models picked that do not present efficiency enough. In conclusion, experimental animal models are able to bring relevant information about the course of ocular toxoplasmosis.

Keywords: experimental model, ocular toxoplasmosis, animal model

1. Introduction

Toxoplasma gondii was first described in 1908 by Nicolle and Manceaux, presented into tissues of a north-African rodent, known as *Ctenodactylus gundi*, which after was mentioned to describe the specific epithet that compose specie. Simultaneously in Brazil, Splendore identified same parasite in rabbit tissues. *T. gondii*, etiological agent of toxoplasmosis and an obligatory intracellular parasite, affects different species of vertebrates and invertebrates. In addition, *T. gondii*

presents three different infective forms that can infect hosts by ingestion of raw meat containing cysts or, food and water containing oocysts [1]. Infection can also affect the embryo, during pregnancy; with different levels of severity, depending on the specie and the period that infection occurs. Toxoplasmosis can present different manifestations, as fever, increase of lymph nodes, intraocular inflammation [2], encephalitis, and other systemic infections [3].

Ocular toxoplasmosis, a vision-threatening ocular disease, is the most common cause of infectious uveitis [4]. It is one of the mean manifestations of toxoplasmosis in humans, affecting up to 30% of the humans worldwide. In Europe and North America, development of ocular toxoplasmosis is around 2% of infected individual. In Brazil, uveitis is estimated to be caused by toxoplasmosis in 60–85% of lesions cases [5]. Highlighting Erechim, Southern Brazil with a high frequency of humans infected usually transmitted by ingestion of uncooked meat containing cysts [6]. Ocular toxoplasmosis was first described in 1923 by Jankû, and subsequently by Levaditi in 1928. Whereas it was just in 1952 that *T. gondii* had its relation to the retinochorioiditis Foerster in Weiss and Kim [7]. Accordingly, some authors, retinochorioiditis is a major cause of visual impairment in the USA, where it accounts around 30–50% of all cases of uveitis [8]. Otherwise many aspects of ocular toxoplasmosis still await answer.

One of the major factors limits is the difficult to obtain human infected material. Once *T. gondii* had a predilection by nervous tissues, locating itself in immune competent individuals in brain and eyes. So, it does necessary experimental animal models. But, animal models do not express reality of human disease. Therefore, the establishment of an ideal experimental model, that mimic the course of ocular toxoplasmosis, is fundamental as a springboard for finding answers of the disease. Considering particularities of each experimental animal model for each specific conduced study.

2. Ocular toxoplasmosis

Accordingly literature, the *T. gondii* reaches the bulb of the eye using the blood, normally causing a focal lesion and asymptomatic, but not well comprehended [9]. The eye is an immunologic privileged environment, as the brain. But, brain barrier is more studied than ocular barrier [10]. In previous studies, ocular toxoplasmosis infection has been formed principally by lymphocytes B. This increase in migration of lymphocytes is associated to high levels of IFN-γ and IL-6 and low levels of IL-10, suggesting that cytokines alterations provide inflammation and retinochorioiditis. Other studies indicate that the severity of ocular toxoplasmosis is close related to intensity of inflammation and presence of IL-17. Thus toxoplasmosis infection relates pathogenesis to Th1 and Th17 cell. While IL-10, TGF-β, and IL-27 are cytokines with an important role into immune regulation of maintenance and inflammation of important sites, as eye environment [5, 7].

The most affected structure in ocular toxoplasmosis is the retina. Retina is the nervous tissue of the bulb of the eye, responsible for transduce photon stimulus into electric impulse. And

http://dx.doi.org/10.5772/67947

for that transduction occurs, it is necessary that the integrity and well function of the 10 layers of retina tissue, identified in **Figure 1**, from the inner tissues to outer in the following order: inner limiting membrane, nerve fibers layer, ganglion cells, inner plexiform, inner nuclear layer, outer plexiform and nuclear layers, outer limiting membrane, segments of photoreceptors, and retinal pigmented epithelium. In evidence, toxoplasmic retinochorioiditis affects straight the retina as a structure, but most damaged layers are nuclear plexiform and ganglion layers, as well as the segments of photoreceptor, once RPE presents a migration, causing a discontinuity forming great interstitial lacunae. Also is observed inflammatory cells in the inner plexiform layers, also responsible for none well function of retina tissue [11].

The retina is the first area involved, furthermore choroids, vitreous humor, and anterior chamber might be also involved, but never will it happen before retina. The most common sign of acute ocular toxoplasmosis is a focal and in major times, unilateral retinal lesion [12].

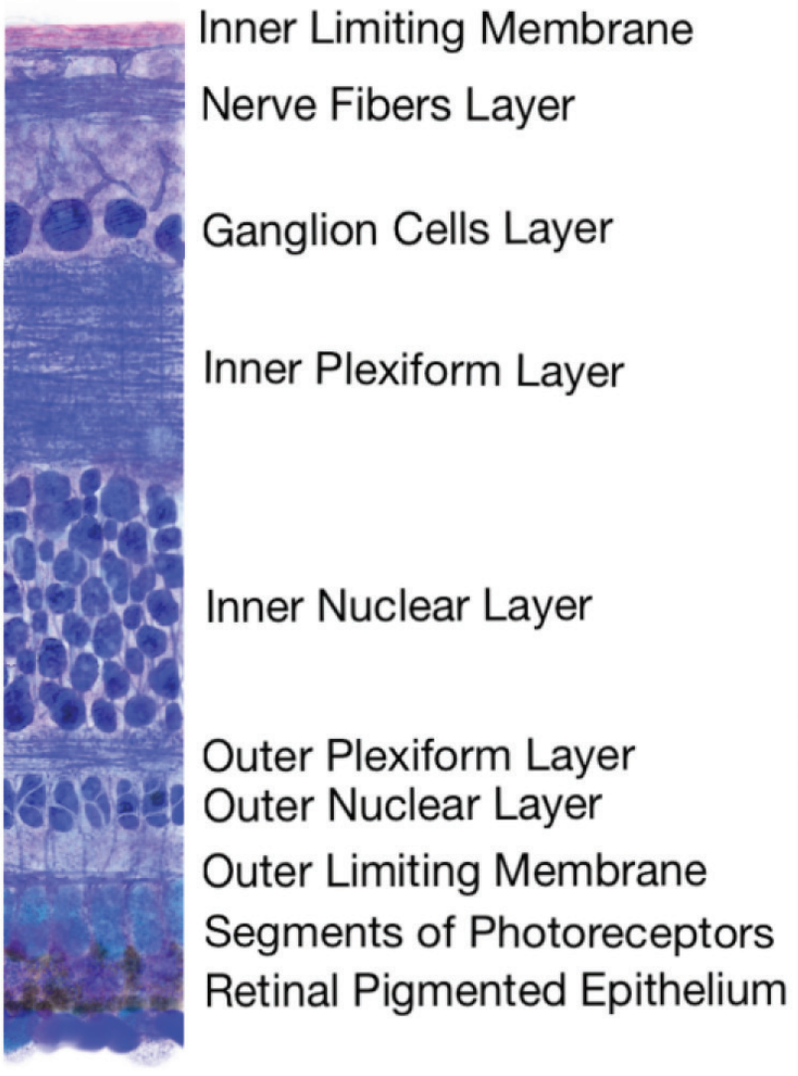

Figure 1. Retinal scheme containing 10 layers that compose this tissue.

But, in some individuals it was observed too, bilateral lesion, occlusive vasculitis, diffuse necrotizing retinitis and scleritis. Retinochorioiditis is commonly observed in congenital and acquired toxoplasmosis [13] resulting in acute disease and infection reactivation. It is possible to affect one or both eyes, presenting it in three different forms. Forms can be didactically differentiated (**Figure 2**) as punctual, multiple, and satellite lesions. In other worlds, punctual lesion might indicate primary infection, while multiple and satellite lesions, might indicate reactivation of disease. In addition, satellite lesions it is characterized by a combination of an active lesion with a healed retinal scar [10]. By the way, it is not dependent if it is acquired or congenital toxoplasmosis [4].

Clinical finds may be influenced by clonal type of *T. gondii*. There are three predominant clonal types, based on virulence studies [14]. But virulent strains appear to have their origin in one genetically homogeneous lineage. Studies based one murine model infers that type II would be responsible for the majority of ocular lesions. Furthermore, recent studies shows that type I, is atypical and with an important role in ocular lesions [14–16]. In Europe, type II strains are responsible for majority of human infections. In South America, a recombinant strain is associated to ocular toxoplasmosis [4]. Studies of Howe and Sibley, in 1995 and Belfort-Neto and collaborators in 2007 correlate type II with an important role in acquired infection, while type I clonal lineage may be responsible for the congenital toxoplasmosis, even so type I and atypical strains may play a role in acquired infection [14]. For instance, type III has been reported only 9% of toxoplasmosis patients in France and United States [17]. However, even with few information relating clonal type with virulence and frequency, just an insufficient part is known, needing more studies in this area.

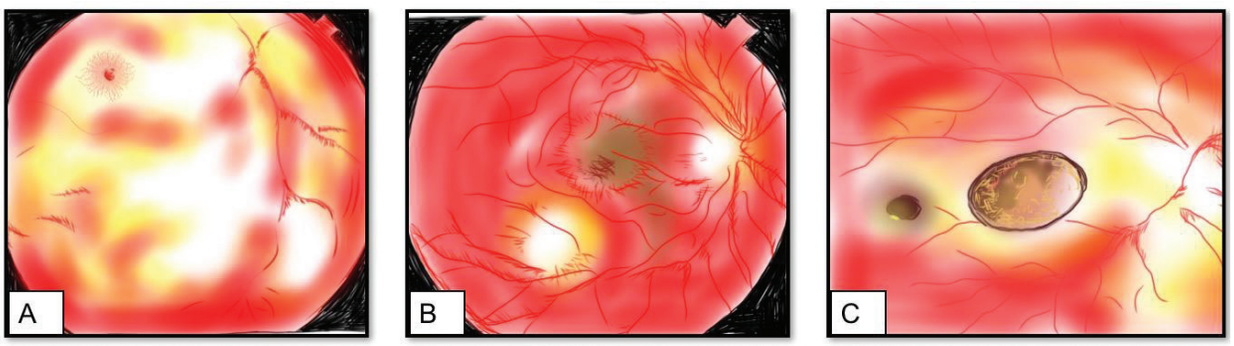

Figure 2. Ophthalmoscopy scheme differentiation of retinal lesions; (A) punctual lesion; (B) multiple lesions; and (C) satellite lesion.

3. Acquired toxoplasmosis

Acquired toxoplasmosis occurs principally for ingesting of raw meat, vegetables, and water contemned with oocysts of *T. gondii*. Acquired toxoplasmosis normally can affect the eye in acute form, beyond 10% of the cases, but the majority is naïve, transitory, and frequently asymptomatic [18]. Loss vision in acquired toxoplasmosis is normally due from destruction of retina tissue, specially the macula. Furthermore, might be worse by reactivation, months or years after [19].

http://dx.doi.org/10.5772/67947

4. Congenital toxoplasmosis

Congenital toxoplasmosis is a result of an infection in prenatal presenting clinic morphologies before birth, or just along the first quarter of gestational period, been present in the forms of anencephaly, hematological abnormalities, loss vision, and blindness or even death [4, 20]. But the majority of manifestations are rare, been subclinical at birth. It can be possible to present lesions along the life. Congenital ocular toxoplasmosis can present itself neonatal, or lately, but it is more common in the last quarter of gestational period. Retinal destruction is a very frequent sequel of congenital disease [8] presenting a predilection for macular involvement [4]. A congenital ocular lesion appears to be the highest risk of systemic infection when compared to acquire ocular toxoplasmosis. Congenital ocular toxoplasmosis has been estimated to affect 3000 kids born in the USA each year. It affects 70–90% of patients, been the most common manifestation of disease. By the way, great majority of kids appears asymptomatic. Report cases indicate that some of them develop chorioretinal lesions, from scars until vision loss [7].

5. Experimental models of ocular toxoplasmosis

First animal model of toxoplasmosis was guinea pig, established by Markham in 1937. But just in 1951, the first animal model for ocular toxoplasmosis was established by Hogan, using intracarotid injection in rabbits. Following same lineage, in 1953, Frenkel managed an intraperitoneal injection in hamster. Lately nonhuman primates, cats, pigs, and dogs started been used as model [4]. Accordingly history of experimental animal models for toxoplasmosis, author and method used exposed in following time line (**Figure 3**).

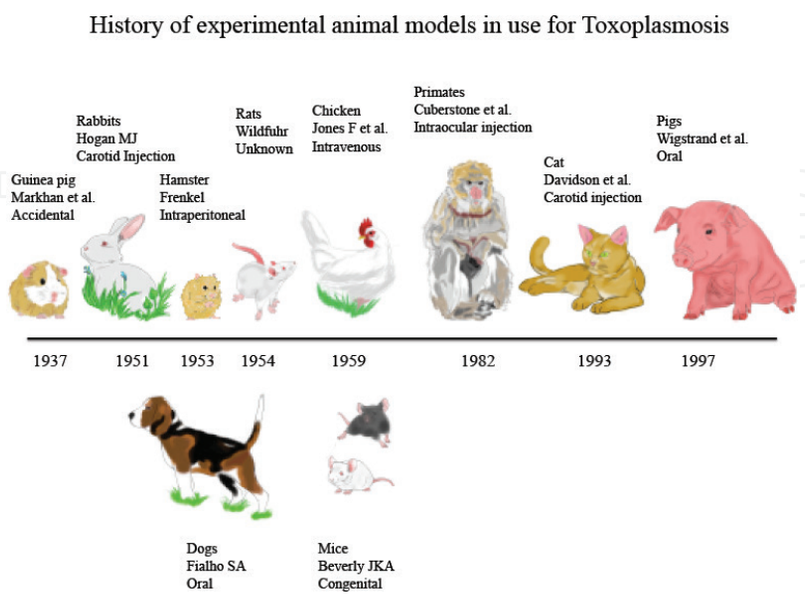

Figure 3. Schematic time line with historic of experimental animal models for toxoplasmosis, independent on development of ocular toxoplasmosis.

In impossibility to obtain sample from human with acute ocular infection, animal models has been developed to supply and find answers [4]. In spite of, any animal model of ocular toxoplasmosis must consider some criteria: parasite entry, onset of disease and manifestation, self-limitation of ocular inflammation, and model of recurrence, parasite strain used, and experimental manipulation of disease processing and treatment [10]. Ocular toxoplasmosis animal models should answer how disease happens in humans, as close as possible, from entry of parasite to development of disease. Furthermore, strains of parasite is so important as route of infection, once some strains show certain defect achieving system of host. The most used strains are: RH, ME-49, Beverly, PLK, and Fukaya. Strains from type I was isolated from patients and animals. Type II lesser extent type I strains are used in animal models of ocular infection.

T. gondii parasitizes the host, without producing clinical disease. After penetrating intestinal epithelial cells. *T. gondii* may spread to other organs by lymphatics and blood system, multiplying in any cell of the organism. As long *T. gondii* may cause an infection and severe disease in animals, causing great losses in some species, like sheep and goats, generating embryonic death, abnormalities, and others.

It is important to highlight that toxoplasmosis affects individuals in different forms, and in some cases do not express the disease how it is described in literature, otherwise it is of major importance to express how parasite is able to hand on the intermediate and definitive host. In immunosuppressed host, toxoplasmosis may lead them to death, unless accomplished of correct treatment. Actually known as corticosteroid, sulfadiazine, and pyrimethamine. Those medics relapse disease, doing necessary in some experimental models. Besides, pathogenicity of *T. gondii* is determined by virulence of the strain and resistance of the host, in some cases even hosts habits.

Nowadays, it is known that some variation of mice is more susceptible than other, seeing the severity of infection course. Adult rats do not become ill, differently from the youngers from the same species, which can dies of toxoplasmosis. Ungulates are the most resistant hosts to toxoplasmosis, whereas some marsupials, and nonhuman primates are highly susceptible to *T. gondii* infection [21]. In literature animals like pig, ordinarily there are not many descriptions as experimental models, moreover as case report. Like young pigs, which have high mortality, while adult pigs are resistant. Notwithstanding, infected pigs are described with pneumonia, myocarditis, encephalitis, and placental necrosis. Other species as mink, rabbits, birds, and other domesticated and wild animals, show sporadic and widespread outbreaks of toxoplasmosis [22]. Many authors have described toxoplasmosis in different species along the years, and this allows conclude how spread is toxoplasmosis.

Retinochorioiditis in laboratory animals may vary, because interferences with parasite proliferation and viability, and the inoculation route (perioral, intraocular, intraperitoneal, conjunctival, or parenteral administration [23].

6. Methods of infection

Any experimental animal model of ocular toxoplasmosis has a set of specific features: specie, parasite strain, stage and concentration of parasites per milliliter of the inoculum, and infection

route. Also important, parasite entry must be rigorously chosen. Parasite entry groups: intracarotid injection; intraperitoneal and oral infection, and presents different recurrences of the disease. Intracarotid injection is performed in bigger experimental models like nonhuman primates, cats, and rabbits. Animals must be anesthetized, accordingly Institutional Animal Care and Use Committee, and the right common carotid artery has to be isolated surgically. Using a 27-gauge hypodermic needle, the inoculum must be performed [24].

Intraocular injection allows purport an ocular toxoplasmosis, and has been used in nonhuman primates, guinea pigs, rabbits, and mice. It is possible to perform intracamerally, periretinally, or intraretinally. The disadvantage of this method is that it can cause mechanical damage to retina, which may interfere in results of the course of the disease. First experiments, using this method consisted on retinal injections through the pars plana, crossing the vitreous cavity. Before introducing needle it was necessary a sclerotomy in the pars plana. Place where the needle was introduced [25]. Notwithstanding, administration by instillation, consist of an application over the surface of the eye, and it has shown close results to intraocular injection and in addition maintains integrity of ocular tissue [2]. Instillation is conduced using one drop of solution containing a determined concentration of parasites directly on eye surface.

The most used method, intraperitoneal injection consists of an inoculum inside the peritoneal cavity. This method is easy to perform and successfully leads to ocular toxoplasmosis and, it has many reports in hamsters and mice. Perioral via is described in literature, by introducing a solution containing oocytes in determined concentration inside the mouth of the animal. Equally important gavage is executed with an instrument that certified that experimental animal model received the right dosage, introducing a solution containing oocytes direct into the stomach of experimental model. But it does not reproduce the ocular toxoplasmosis in majority of cases, further results, or depending on the strain no result. Nevertheless performing perioral demonstrated promising results. For congenital ocular toxoplasmosis experimental models, still been an inoculum in pregnant mice, or embryonated eggs. Normally, pregnant mice are infected via intraperitoneal or perioral. Alternatively, an injection of Tachyzoite free forms in embryonated eggs, allow simulating directly embryo infection.

7. Diagnose in experimental model

In experimental model, identification of toxoplasmosis can be made finding *T. gondii* cysts into the biopsies, with a specific color reaction and immunohistochemical, or polymerase chain reaction (PCR) technique [13]. Nowadays, PCR is used even when is not found the cysts on biopsies. Diagnose of toxoplasmic retinochorioiditis in experimental animal model, is already described in literature, as a combination of three techniques: ELISA, PCR, and immune-staining. By the way, PCR has been replaced by real-time PCR (qPCR), that increases the sensibility of diagnose in 97% and considers that results are further than PCR [14]. Eventually, enzyme-linked immunosorbent assay (ELISA) is one of the most used tests, identifying immunodominant antigens during *T. gondii* infection. However, it can be used only as a complementary diagnose, once identify antigens and not the parasite. Actually, ELISA has been replaced by

flow cytometry. Flow cytometry allows to measure the concentration of substances further and in a less sample dilution. Besides, nowadays there are some specific commercial kits that provide good results, multianalyses in a short period.

8. Guinea pig model

Guinea pigs were one of the first experimental animal models used for this purpose, in an accidental experiment [26]. While working with the submaxillary gland virus of guinea pigs, Markham had noted that some of animals were dying after experiments. Asymptomatic and temperature abruptly fell. However, they have rarely been used for further investigation of the disease after first experiments, with little information about. In a study of acquired transmission, a conjunctiva penetration of tachyzoites in this model was preceded, and authors found invasion of conjunctiva epithelia and goblet cells within 15 minutes post infection [27]. Replicating study within 4 hours was possible to identify a high concentration of antibodies. In conclusion, *T. gondii* evokes a mild to moderate inflammatory response. In spite of, the instillation and infection perioral have associated lymphoid tissue, been considered part of the mucosal immune system, and invasions mimic the three forms of parasite forms (tachyzoites, bradyzoites, and sporozoites). In accordance with previous studies, guinea pig might be a good experimental animal model of ocular toxoplasmosis, once it is susceptible to *T. gondii* infection and also it is resistant to great number of parasites [28].

9. Rabbit model

Rabbits are known to have a genetically determined low resistance against infection. With exacerbated inflammation accordingly to virulence and antigenicity of the parasite strain. Toxoplasmosis in this animal model was described first by Hogan in 1951 [29]. Infection with RH strains is able to produce chorioretinal lesions similar those described in cats and humans, however, concomitantly meningoencephalitis and rapid death. This describe how susceptible is this model. The most common route of infection in this experimental animal model is intravitreal inoculum, developing retinochorioiditis, equally in nonhuman primates. In rabbits as the same in nonhuman primates model is possible to observe pigmented scars after disease remission.

Intraocular infection combined with ophthalmoscopy in rabbits is easy to perform. The infection is described as a dissemination of retinochorioiditis, vitreal infiltration, and retinal detachment [30]. First affecting retina before choroid, differing from *Felidae* model. By the way, this route of infection might cause some trauma in the ocular tissue interfering on results. Instillation on the ocular surface must supplant best this method. In studies, which were described perioral infection, animal model presented low seroprevalence, and did not presented parasites, when histologically analyzed. Tissues like brain, diaphragm, and heart are considered the most damaged. But with no ocular signal described.

10. Hamster model

As experimental model, hamsters had experimental ocular toxoplasmosis, described by Frenkel in 1953 [31], using RH strains showed necessity of therapy while CJ did not generate ocular lesions. In fact the use of ME-49 strains do, intraperitoneal or perioral may influence on ocular toxoplasmosis [7].

Golden Hamster, when infected with RH or CJ strains of *T. gondii*, normally presents sporadic ocular disease, and without treatment with sulfadiazine and pyrimethamine, animals succumb to encephalitis. In contrast, when using ME-49 strain, Golden hamster became an excellent model for ocular toxoplasmosis [32]. Disease may vary among hamsters, but all develop ocular disease, usually limited to retina with loss of layers. All the animals can develop in both eyes the disease among 2 or 3 weeks post inoculum, resolving spontaneously over time, as in humans. As an advantage, eye of this model are large enough to allow fundus photography, in spite of lesions are different from humans, becoming bilateral and multifocal. Hamsters infected orally show development of ocular toxoplasmosis within 4–8 weeks after infection even when intraperitoneal infection is performed, causing retinochorioiditis. Therefore, hamster's disease does not result in pigmentation, showing itself atrophic and bilateral [7].

11. Dog model

There are few studies in experimental dog model, but Fialho's study is one of the first studies using dogs as experimental models, with mean alterations: ocular lesions [33]. In dogs are present retinitis, choroiditis and pseudocyst in ciliary epithelium [34]. During days post inoculation, there was only as a clinical sign a submandibular lymph node enlargement. Considering that gavage, intraperitoneal and intravenous demonstrated similar finds. With nonrelevant difference. Indicating that the immune response was observed in all animals. Similar to humans, dogs present ocular toxoplasmosis evolution from simple papillary edema to blindness and ocular necrosis. Morphological alterations in this experimental model are highly considered, once in humans are described in literature as late manifestation of toxoplasmosis, acquired or congenital. It is also demonstrated in experimental dog model [34]. Accordingly author's results can be reproduced in only 30 days. Turning dogs excellent experimental models. By the way, its maintenance and costs turn this experimental animal model expensive and labored. Once it is seem as a pet animal. Not been easily accepted as an experimental model, for the society and committee for the use of laboratory animals.

12. Murine model

In majority toxoplasmosis in murine model, shows itself as asymptomatic, and widely prevalent, but clinically is relatively rare [21]. They are easily accessible, with complete genome sequenced, exist many knock-outs and a large number of immunological reagents available.

Beverly JKA introduced mice as animal model in 1959, for congenital experiments [35]. Furthermore, it presents certain resistance to toxoplasmic encephalitis that is controlled by gene action. On the other hand, some vary lineage, like C57BL/6 do not have this haplotype generating spontaneously eye lesions [8]. C57BL/6 shows a high parasite load after 7 days of reinfection associated with deterioration of retinal architecture. When mice are infected by instillation or intraocular injection, both methods unleash ocular toxoplasmosis. Highlighting that instillation must replace with excellence infection of bulb of the eye, obtaining in a short period of time an infection, approaching in 7 days [2]. Considering period of obtaining results, NMRI mice infected, with same strain of *T. gondii* demonstrate bilateral ocular toxoplasmosis in 14–21 days, while Swiss-Webster mice, parasite loads did not peak upon reinfection. BALB/c is considered resistant to the infection, showing itself as asymptomatic. In the same way, it must be noticed that diagnosis of migrant of retinal pigmented epithelium is more difficult in albino mice. Otherwise murine congenital toxoplasmosis there is significant opaque cataract formation [7].

Rats as an experimental model described by Wildfuhr, in 1954 [36], but with little information about this author's studies, present high resistance to toxoplasmic infection, because of this, that experimental animal model is used only when compared to human adults disease.

Murine model mimics likely time of exposure, establishment of cysts in humans and is easy of manipulation. Instead, it has the disadvantages of producing different degrees of severity and ocular lesions and hard monitoring, because of size of the eye [24]. Hence with many advantages, murine model may offer a great spread of methods and variable results, but it is necessary such a great number of animals to perform statistically relevant analyses.

13. Bird model

As a natural host of *T.* gondii, chicken was first described as an experimental model for toxoplasmosis in 1959 by Jones et al. [37]. Level of infection in chicken may be under detectable levels, and low parasitemia makes diagnosis in this model by microscopy difficult, needing ELISA or more sensible methods [38]. In some studies, already has been demonstrated that dose of parasites influence on studies, finding parasites in liver and heart, but none was found in brain cells. Doses higher than 10^3 parasites per milliliter, showed high mortality, indicating in these case lower dosages. Many species of birds can act as a reservoir for *T. gondii*, apparently with or without symptoms [39]. But some studies relating to gender prove that female chicken present more seroprevalence than male, probably associated to behavior manner [38].

On the other hand, embryonated eggs have actually shown itself as good model to test pathogenicity of strains of *T. gondii*, but not all animals in study have demonstrated alteration in ocular structure. Embryos of chicken are able to reproduce projections of retinal layers, detachment of retinal pigmented epithelium, alterations in disposition of photoreceptor, inflammatory infiltrate and alteration in gene expression, important for the development of retina [40].

It is also possible to see migration of RPE, suggesting a potential role of RPE phagocytosis. Evolution of retinochorioiditis in embryo models is related to the period of infection and strain of parasite, and it has a major tachyzoites proliferation in last periods [23].

Chicken embryo has shown itself, as an excellent performance when compared to other congenital ocular toxoplasmosis animal model, although does not exclude them. Its maintenance, usability, stereo environment, and easy to obtain, qualify this model as a great experimental model [40] and can present great studies when correlated to the control of environmental contamination, by controlling prevalence of infected chickens [38].

14. Nonhuman primate model

This experimental animal model of ocular toxoplasmosis, was first described in a bid of replace rabbit model proposed by Nozik and O'Connor in 1968 [25]. First experiment in this model was described using intraocular inoculum containing RH strains of *T. gondii*, even so it was possible to mimic a retinochoroidal inflammation, there was not retinal necrosis, with no evidence of systemic illness, not even detachments of retinal layer. In nonhuman primates, it is possible to see a remission of the disease [10]. Furthermore, intraretinal infection is easy to perform in monkeys, and ophthalmoscopy can easily be done due to the size of eye of this experimental model. In spite of, it is already known that New world monkeys, *Carabide* are highly susceptible to clinical toxoplasmosis when compared to Old world monkeys, as *Cercopithecide*, that present itself resistant. Monkeys from the Old world seem resistant to infection comprehending that it might not been a good experimental model for ocular toxoplasmosis, whereas monkeys from New world look like useful. In contrast, as a disadvantage, these experimental animal models are costly and require proper housing conditions, which sometimes cannot be granted in most laboratories.

15. *Felidae* model

Clinical toxoplasmosis has been diagnosed in wild *felidaes* but, in great majority of cases, the parasite was identified only in feces. First report of cats as experimental model was made in 1993 by Davidson et al. Cats were infected via carotid injection containing ME-49 strains of *T. gondii*. This experiment induced an increase in rectal temperature, and focal areas of choroidal and retinal inflammation, highlighting bilateral lesions. Equally important within 4 weeks, blood-retinal barrier has been established in most posterior segments lesion. Unlike humans, choroiditis is more pronounced in this model than retinitis during the course of the disease. Another relevant information about this model is that oocysts are detectable in feces from 24 days post inoculation but with a low reproducibility [24].

In addition, an advantage of this method of infection for this experimental model is the low concentration of tachyzoites inoculated via carotid, showing retinal inflammation, different

from human. In humans, this characteristic is about a reactivation of congenital infection, multifocal, and self-limiting.

Routes of inoculation as subcutaneous and intraperitoneal, performed with a large number of tachyzoites of RH strains, leads cat too fast to death. Oral administration produces only sporadic ocular lesions, but has shown as not a good via. After exposure, there is dissemination of *T. gondii* to various extraintestinal tissues, like in humans, but most cats present immunity development and express disease only when immune-suppressed or immune-competent. It can present itself as a good model for understanding biology of parasite, but do not understand disease in humans [24].

16. Pig model

Pigs present a potential infection for humans, from eating under-cooked meat [22]. This experimental animal model infected orally [41] or by intramuscular injection presented apathetic and lethargic among 2 and 9 days post infection. Besides, it is possible to see some aggressiveness attitude during chronic phase. By the way, nonlesion was allowed to identify. Using RH strains of *T. gondii*, animals can present eye discharge and temperature embracing form of *T. gondii*. When using ME-49 strains, this experimental animal model demonstrated increase in band neutrophils. Even those neutrophils are not crucial for toxoplasmosis control; but seem to exert some important role during ocular toxoplasmosis infection, when compared to RH strains immune response. RH strains trigger a lower immune response than ME-49. On the other hand, ME-49 strains reach blood system faster by perioral method than RH via intramuscular inoculum, and can mimic the biological activity of parasite as in immunocompromised humans chronically infected, indicating that the pig experimental model may be a good model to understand chronic toxoplasmosis in immune competent humans [42].

17. Sea mammals model

Many sea mammals are described with toxoplasmosis. In Philadelphia, at a zoo, a case of a sea lion that has died was discovered during necropsy, with cysts of *T. gondii* in heart and stomach. In 1985, a fur seal died of toxoplasmic encephalitis. More after serological studies reported a prevalence of 7.6% of toxoplasmosis in harbor seals and dolphins in Canada. Thereafter, congenital toxoplasmosis was reported in sea mammals in Australia and in Beluga whales from an estuary at St. Lawrence. In general, there are many case reports in this model. Furthermore, there are no relevant study using sea mammals as experimental models for ocular toxoplasmosis, but they might be, an important fount of information for controlling marine infection of environment. Previous studies suggest that coastal pollution from human activities is a source of *T. gondii*. Actually, concentration of oocysts by shellfish can occur, and once sporulated, oocysts can survive in marine water for a long period of time, turning shellfish a source of infection to marine environment [22].

http://dx.doi.org/10.5772/67947

18. Ungulates model

Since 1992, ungulates and nondomestic ruminants have been reported clinically; at the same time, nonexperimental study describes clinically infection by toxoplasmosis. Actually, reports of a *Saiga antelope*, deer, and other animals showed fatal in these cases. Otherwise, there is no report of ungulates as pronghorn, once it is highly susceptible to *T. gondii* infection [22]. Expressing that ungulates are not good experimental models for toxoplasmosis, once it is extremely sensible to this protozoan infection.

19. Marsupials model

Toxoplasmosis is a serious disease of Australian marsupials, local zoo report countless death, as suddenly die, without clinical or neurological signs, loss of vision, diarrhea, or respiratory distress. Virtually any organ can be affected [43]. Even so, some species of wallabies were identified with high levels of antibodies, like adult black-faced kangaroos, this allows to comprehend that not all exposed wallabies die of toxoplasmosis. But, some tests of vaccine (S-48) with live, or modified and nonpersistent strain of *T. gondii* showed itself lethal in Tammar wallabies, describing how susceptible is this specie. Marsupials as New World Monkeys look to be unusually susceptible to toxoplasmosis [7]. Actually the approach is preventing contamination of food and water, needing more studies that are able to immunize those models, with no founds until now [22].

20. Conclusion

Experimental animal models do not express disease how it happens in humans. However, they are able to bring relevant information about the course of ocular toxoplasmosis. Mice in general are the most usual models nowadays. Adult birds do not express the disease, being a reservoir with no clinical manifestation, but avian embryos allow studies about congenital ocular toxoplasmosis, while hamsters provide information about infection. Nonhuman primates, instead the route of infection, may present important facts of the disease, while cat as the definitive host also presents ocular alteration. Other models do not have experimental description, by the way, case report help to fill the blanks for new contributions of methods, experimental model, and strain of parasite. The choice of an ideal experimental animal model is extremely important to understand and contribute for improvements on prospective treatments.

Author details

Aléx Martins Nasaré* and Roberto Carlos Tedesco

*Address all correspondence to: alex.nasare@hotmail.com

Federal University of São Paulo, São Paulo, Brazil

References

[1] Jones LA, Alexander J, Roberts CW. Ocular toxoplasmosis: in the storm of the eye. Parasite Immunology. 2006;28:635–642.

[2] Tedesco RC, Smith RL, Corte-Real S, Calabrese KS. Ocular toxoplasmosis in mice: comparison of two routes of infection. Parasitology. 2005;131:303–307. DOI: 101017/S003118200500781X

[3] Dubey JP. Advances in the life cycle of *Toxoplasma gondii*. International Journal of Parasitology. 1998;28:713–717.

[4] Dukaczewska A, Tedesco R, Liesenfeld O. Experimental models of ocular infection with *Toxoplasma gondii*. European Journal of Microbiology and Immunology. 2015;4:293–305. DOI: 10.1556/1886.2015.00045

[5] de Souza W, Belfort Jr. R. Toxoplasmose e *Toxoplasma gondii*. 1st ed. Rio de Janeiro. Editora: Fiocruz. 2014. pp. 181–196. ISBN: 978-85-7541-437-8

[6] Belfort-Neto R, Nussenblatt V, Rizzo L, Muccioli C, Silveira C, Nussenblatt R, Khan A, Sibley LD, Belfort Jr. R. High prevalence of unusual genotypes of *Toxoplasma gondii* infection pork meat samples from Erechim, Southern Brazil. Annals of the Brazilian Academy of Sciences. 2007;79:111–114.

[7] Weiss LM, Kim K. *Toxoplasma gondii:* the model apicomplexan – perspective and methods. 2nd ed. Massachusetts. Academic press. 2013. pp. 161-192. ISBN: 978-9-12-39648 1-6

[8] Roberts F, McLeod R. Pathogenesis of toxoplasmic retinochoroiditis. Parasitology Today. 1999;15:51–57. DOI: 10.1016/S0169-4758(98)01377-5

[9] Bossi P, Caumes E, Paris L, Dardé M, Bricaire F. *Toxoplasma gondii*-associated Guillain Barré syndrome in an immunocompetent patient. Journal of Clinical Microbiology. 1998;36(12):3724–3725.

[10] Maenz M, Schlüter D, Liesenfeld O, Schares G, Gross U, Pleyer U. Ocular toxoplasmosis past, present and new aspects of an old disease. Progress in Retinal and Eye Research. 2014;39:77–106. DOI: 10.1016/j.preteyeres.2013.12.005

[11] Tedesco RC, Smith RL, Corte-Real S, Calabrese KS. Ocular toxoplasmosis: the role of retinal pigment epithelium migration in infection. Parasitology Research. 2004;92:467–472. DOI: 10.1007/S00436-003-1031-2

[12] Holland GN, O'Connor GR, Belfort Jr. R, Remington JS. Toxoplasmosis. In: Pepose JS, Holland GN, Wilhelmus KR. Ocular infection and immunity. St. Louis: Mosby. 1996. pp. 1183–1223.

[13] Arcelus MP, Salinas A, Layana AG. Manifestaciones retinianas de las enfermedades infecciosas. Anales del Sistema Sanitario de Navarra. 2008;31:57–68.

[14] Commodaro A, Belfort RN, Rizzo LV, Muccioli C, Silveira C, Claudio JR, Burnier MN Jr., Belfort R. Ocular toxoplasmosis – an update and review of the literature. The Memórias do Instituto Oswaldo Cruz. 2009;104:345–350.

[15] Dubey JP, Graham DH, Blackston CR, Lehmann T, Gennari SM, Ragozo AMA, Nishi SM, Shen SK, Kwok OCH, Hill DE, Thulliez P. Biological and genetic characterization of *Toxoplasma gondii* isolates from chicken (*Gallus domesticus*) from São Paulo, Brazil: unexpected findings. International Journal of Parasitology. 2002;32:99–105.

[16] Dubey JP, Jones JL. *Toxoplasma gondii* infection in humans and animals in the United States. International Journal of Parasitology. 2008;38:1257–1278.

[17] Nowakowska D, Colón I, Remington JS, Grigg M, Golab E, Wilc-zynski J, Sibley LD. Genotyping of *Toxoplasma gondii* by multiplex PCR and peptide-based serological testing of samples from infants in Poland diagnosed with congenital toxoplasmosis. Journal of Clinical Microbiology. 2006;44:1382–1389.

[18] Nussenblatt RB, Whitcup SM. Uveitis: fundamentals and clinical practice. 4th ed. San Louis: Mosby. 1996. p. 480.

[19] Petrilli AMN. Uveítes na infância [thesis]. São Paulo: Escola Paulista de Medicina. 1987.

[20] Holand GN. Ocular toxoplasmosis: a global reassessment. Part I: epidemiology and course of disease. American Journal of Ophthalmology. 2003;136:973–988.

[21] Dubey JP, Beatie CP. Toxoplasmosis of animals and man. Boca Raton: CRC press. 1988. p. 220. ISBN: 0849346185

[22] Hill DE, Chirukandoth S, Dubey JP. Biology and epidemiology of *Toxoplasma gondii* in man and animals. Animal Health Research Reviews. 2005;6(1):41–61. DOI: 10.1079/AHR2005100

[23] Moraes AMM, Pessôa CN, Vommaro RC, de Souza W, de Mello FG, Hokoç JN. Cultured embryonic retina systems as a model for the study of underlying mechanisms of *Toxoplasma gondii* infection. Investigative Ophthamology and Visual Science. 2004;45:2813–2821.

[24] Davidson MG, Lappin MR, English RV, Tompkins MB. A feline model of ocular toxoplasmosis. Investigative Ophthalmology and Visual Science. 1993;34:3653–3660.

[25] Culbertson WW, Tabbara KF, O'Connor GR. Experimental ocular toxoplasmosis in primates. Archives of Ophthalmology. 1982;100:321–323.

[26] Markham FS. Spontaneous Toxoplasma encephalitis in the guinea pig. American Journal of Hygiene. 1937;26:193–196.

[27] Pavesio CE, Lightman S. *Toxoplasma gondii* and ocular toxoplasmosis: pathogenesis. British Journal of Ophthalmology. 1996;80:1099–1107.

[28] Skorich DN, Chiappino ML, Nichols BA. Invasion of the guinea pig conjunctiva by *Toxoplasma gondii*. Investigative Ophthalmology and Visual Science. 1988;29(12):1871–1880.

[29] Hogan MJ. Ocular Toxoplasmosis. New York: Columbia University Press. 1951.

[30] Garweg JG, Kuenzli H, Boehnke M. Experimental ocular toxoplasmosis in navie and primed rabbits. Ophthalmology. 1998;212:136–141.

[31] Frenkel JK. Ocular lesions in hamsters with chronic Toxoplasma and Besnoitia infection. American Journal of Ophthalmology. 1955;39:203–225.

[32] Pavesio CE, Chiappino ML, Gormley P, Setzer PY, Nichols BA. Acquired retinochoroiditis in hamsters inoculated with ME 49 strain Toxoplasma. Investigative Ophthalmology Visual Science. 1995;36:2166–2175.

[33] Fialho, S.A. Toxoplasmoseocular: contribuiçãoaoestudo clínico e experimental [thesis]. Rio de Janeiro. Tese (Doutorado em Medicina)—Faculdade Nacional de Medicina da Universidade do Brasil, 1953; p. 139.

[34] de Abreu CB, Navarro IT, dos Reis ACFM, de Souza MSB, Machado R, Marana ERM, Prudêncio LB, Mattos MR, Tsutsui. Ocular toxoplasmosis in young Dogs inoculated with *Toxoplasma gondii.* Ciência Rural. 2002;32(5):807–812. ISSN: 0103-8478

[35] Beverly JKA. Congenital transmission of toxoplasmosis through successive generations of mice. Nature. 1959;4671:1348–1349.

[36] Wildfuhr G. Toxoplasmose. Nature. Jena: Gustav Fischer, Villengang 2. 1954. pp. 176.

[37] Jones FE, Melton ML, Lunde MN, Eyles DE, Jacobs L. Experimental toxoplasmosis in chickens. The Journal of Parasitology. 1959;45:31–37.

[38] Ibrahim HM, Abdel-Gha ar F, Osman GY, El-Shourbagy SH, Nishikawa Y, Kha ab RA. Prevalence of Toxoplasma gondii in chicken samples from delta of Egypt using ELISA, histopathology and immunohistochemistry. Journal of Parasitic Diseases. 2016;40(2): 485-90 DOI: 10.1007/s12639-014-0530-7

[39] Dubey JP. Tachyzoite-induced life cycle of *Toxoplasma gondii* in cats. Journal of Parasitology. 2002;88:713–717.

[40] Nasare AM, Tedesco RC, Cristovam PC, Cenedese MA, Galisteo Jr. AJ, Andrade Jr HF, Gomes JAP, Guimarães EV, Barbosa HS, Alonso LG. *Toxoplasma gondii* infection of chicken embryos causes retinal changes and modulates *HSP90B1* gene expression: a promising ocular toxoplasmosis model. European Journal of Microbiology and Immunology. 2015;5(4):316–320. DOI: 10.1556/1886.2015.00024

[41] Wingstrand A, Lind P, Haugegaard J, Henriksen SA, Bille-Hansen V, Sørensen V. Clinical observations, pathology, bioassay in mice and serological response at slaughter in pigs experimentally infected with *Toxoplasma gondii*. Veterinary Parasitology. 1997;72:129–140.

[42] Miranda FJB, de Souza DB, Frazão-Teixeira E, de Oliveira FC, de Melo JC, Mariano CMA, Albernaz AP, de Carvakho ECQ, de Oliveira FCR, de Souza W, DaMatta RA.

Experimental infection with the *Toxoplasma gondii* ME-49 strain in the Brazilian BR-1 mini pig is a suitable animal model for human toxoplasmosis. The Memórias do Instituto Oswaldo Cruz. 2015;110(1):95–100. DOI: 10.1590/0074-02760140318

[43] Canfield PJ, Hartley WJ, Dubey JP. Lesions of toxoplasmosis in Australian marsupials. Journal of Comparative Pathology. 1990;103:159–167.

IntechOpen

IntechOpen