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Toxoplasmosis: a history of clinical observations

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Abstract

It has been 100 years since *Toxoplasma gondii* was initially described in Tunisia by Nicolle and Manceaux (1908) in the tissues of the gundi (*Ctenodactylus gundi*) and in Brazil by Splendore (1908) in the tissues of a rabbit. *Toxoplasma gondii* is a ubiquitous, Apicomplexan parasite of warm-blooded animals that can cause several clinical syndromes including encephalitis, chorioretinitis, congenital infection and neonatal mortality. Fifteen years after the description of *T. gondii* by Nicolle and Manceaux a fatal case of toxoplasmosis in a child was reported by Janků. In 1939 Wolf, Cowen and Paige were the first to conclusively identify *T. gondii* as a cause of human disease. This review examines the clinical manifestations of infection with *T. gondii* and the history of the discovery of these manifestations.

Keywords

Toxoplasma gondii; Apicomplexa; Clinical disease; History; Symptoms

1. Introduction to the parasite

Toxoplasma gondii is a ubiquitous protozoan parasite that is estimated to infect one-third of the world's human population. It can infect many species of warm-blooded animals and is a significant zoonotic and veterinary pathogen. It is recognized as a category B priority pathogen by the National Institutes of Health, Bethesda, USA. In several of its hosts, *T. gondii* is associated with congenital infection and abortion. In addition, *T. gondii* can cause encephalitis or systemic infections in the immunocompromised, particularly individuals with HIV/AIDS. It has been 100 years since *T. gondii* was initially described in the tissues of *Ctenodactylus gundi*, a North African rodent, by Nicolle and Manceaux (1908). In the same year Splendore (1908), in Brazil, reported on the identification of this organism in the tissues of a rabbit. The genus was named by Nicolle and Manceaux as *Toxoplasma* for its bow-like shape (from Greek: toxo= bow or arc; plasma=creature). Other forms of *Toxoplasma* including tissue cysts were recognized to exist by several researchers including Frenkel and Friedlander (1951), but it was not until the 1960s and 1970s that the parasite was identified as a coccidian. The cat was identified as the definitive host by several groups working independently, including Frenkel

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et al. (1970). Further details of the history of the discovery of the pathogen are described in recent reviews (Ajioka and Soldati, 2007; Dubey, 2007).

In humans, *T. gondii* is commonly acquired by the oral ingestion of tissue cysts containing bradyzoites; however it can also be acquired by the ingestion of oocysts containing sporozoites that are the product of a sexual cycle in cat intestines. Classically, consumption of undercooked meat, particularly pork and lamb, has been ascribed to be the major risk factor for acquisition of toxoplasmosis. Improved animal husbandry practices as well as increased awareness of the risks of consuming undercooked meat have resulted in decreased prevalence of toxoplasmosis world-wide (Tenter et al., 2000). The recognition of waterborne toxoplasmosis in humans has provided another dimension to the epidemiology of this infection (Bowie et al., 1997; Bahia-Oliveira et al., 2003; de Moura et al., 2006; Belfort-Neto et al., 2007). After ingestion, tissue cysts or oocysts invade host cells and differentiate into tachyzoites which divide rapidly within host cells and together with the host's immune response to this pathogen are responsible for the clinical manifestations of infection. Tachyzoites differentiate into latent bradyzoite forms which are surrounded by a carbohydrate-rich cyst wall within the parasitophorous vacuole. This differentiation can be increased by exposure of the organism to stress conditions such as an immune response to the tachyzoites. Tissue cysts can persist indefinitely for the life of the host, perhaps due to a cycle of reaction and re-infection. If an individual becomes immunocompromised these tissue cysts serve as a reservoir from which disseminated or local infections can develop. Tissue cysts have a predilection for neural and muscle tissue as well as the eye in humans, with most cases of reactivation disease presenting as encephalitis or chorioretinitis.

2. Clinical manifestations of *T. gondii* infection

While asymptomatic infection with *T. gondii* resulting in a latent infection with tissue cysts is common in humans, symptomatic infection, i.e. toxoplasmosis, is seen much less frequently. Specific groups of patients including congenitally infected fetuses and newborns, and immunologically impaired individuals are, however, at high risk for severe infection due to this parasite. Congenital toxoplasmosis is a consequence of an immunologically naïve mother acquiring a new infection, which is characteristically asymptomatic, during pregnancy. Congenital infection results in a relapsing disease in infected children. Chorioretinitis is a manifestation of both congenital infection and acute acquired infection (Couvreur and Thulliez 1996; Montoya and Remington, 1996); where it has been seen both sporadically and in the context of an epidemic of acute toxoplasmosis (Montoya and Remington, 1996; Burnet et al., 1998). Immune-deficient patients with defects in T cell-mediated immunity, such as those receiving corticosteroids or cytotoxic drugs, patients with hematological malignancies, organ transplants or AIDS are at high risk for encephalitis or disseminated infections. In such immune-compromised hosts toxoplasmosis is often due to a reactivation of latent infection rather than recently acquired disease. In immune-competent hosts most infections are asymptomatic; however, some individuals do develop chorioretinitis, lymphadenitis, myocarditis or polymyositis. Ten to 20% of cases of *T. gondii* infection in immune-competent adults and children are symptomatic (Remington, 1974). The most common manifestation is asymptomatic cervical lymphadenopathy but any lymph node may be infected. It has been estimated to cause 3 to 7% of clinically significant lymphadenopathy (McCabe et al., 1987). Toxoplasmosis is part of the diagnostic considerations of a case of "mononucleosis" syndrome accounting for 1 to 2% of such cases (Remington et al., 1962). The majority of patients have either Cytomegalovirus (CMV) or Epstein-Barr virus infections. Lymphadenopathy due to *T. gondii* is usually non-fixed, discrete, non-supportive and is not tender (McCabe et al., 1987). Lymphadenopathy may be accompanied by fever, malaise, night sweats, myalgias, sore throat, maculopapular rash, abdominal pain, hepatosplenomegaly and small numbers of atypical lymphocytes (<10%). Symptoms, if present, usually resolve within a few months and rarely

persist beyond 12 months. Rarely, an apparently healthy person develops clinically overt, potentially fatal disseminated disease (Remington, 1974), myocarditis (Montoya et al., 1997; Cunningham, 1982), pneumonitis, hepatitis, myositis (Greenlee et al., 1975) or encephalitis (Remington, 1974). It has been suggested, based on serological surveys and animal behavior studies, that chronic infection with *T. gondii* may be a risk factor for the development of schizophrenia or other behavioral disorders in humans (Yolken and Torrey, 2008).

Toxoplasma gondii is one of the most frequently identified causes of uveitis (Holland, 1999) and is responsible for more than 85% of posterior uveitis cases in southern Brazil (Silveira et al., 1988). Chorioretinal lesions can occur either due to congenital or acquired infection (Montoya and Remington, 1996; Nussenblat and Belfort, 1994). Relapsing disease is frequent, with a median time to recurrence of 2 years. Subclinical, toxoplasmic chorioretinitis may result in complete or partial loss of vision or in glaucoma and may necessitate enucleation (Remington et al., 2001; Halland et al., 1996). Acute chorioretinitis may produce symptoms of blurred vision, scotoma, pain, photophobia, epiphora or loss of central vision. On ophthalmic examination toxoplasmic chorioretinitis presents as white focal lesions with an overlying, intense, vitreous inflammatory reaction that atrophy with healing and develop black pigment. Recurrent lesions tend to occur at the borders of chorioretinal scars and are often found in clusters. The lesions of acute toxoplasmic chorioretinitis due to postnatally or congenitally acquired disease are morphologically indistinguishable.

Acute *T. gondii* infection is asymptomatic in most pregnant women, with the most frequent clinical manifestation of infection being lymphadenopathy. Infection, however, can result in transmission to the fetus and the risk to the fetus does not correlate with symptoms in the mother. Women who have had *T. gondii* infections, i.e. are seropositive, prior to pregnancy are protected from transmitting the infection to their fetuses. Exceptions to this rule have been reported in women with an immune-compromised state (Minkoff et al., 1997) and acute infection occurring shortly before conception (Gavinet et al., 1997; Hennequin et al., 1997; Vogel et al., 1996). Latent *T. gondii* infection may reactivate in HIV-infected women and result in congenital transmission; these infected children usually have HIV as well (Mitchell et al., 1990).

Congenital infection may present as neonatal disease; disease in the first months of life; sequelae or relapse of a previously undiagnosed infection during infancy, childhood or adolescence; or a subclinical infection. Clinical manifestations depend on when the infection was acquired in utero (Reminton et al., 2001). Transmission of infection in weeks 10 to 24 results in the highest severity of clinical disease, whereas transmission in the period of 26 to 40 weeks results in subclinical disease which manifests later in life (Daffos et al., 1988; Desmonts, 1982; Desmonts et al., 1985). If left untreated, 85% of children with subclinical disease develop signs and symptoms of the disease including chorioretinitis or developmental delays (Koppe et al., 1986; Wilson et al., 1980). Transmission and the severity of infection in the child may be modified by providing treatment to the mother during pregnancy (Desmonts and Couvreur, 1979; Forestier, 1991; Hohlfeld et al., 1994; Couvreur et al., 1984). Clinical manifestations of congenital toxoplasmosis vary, but include chorioretinitis, strabismus, blindness, epilepsy, psychomotor or mental retardation, anemia, jaundice, rash, petechiae due to thrombocytopenia, encephalitis, pneumonitis, microcephaly, intracranial calcification, hydrocephalus, diarrhea, hypothermia and non-specific illness (Remington, 2001). Treatment of children with congenital infection can alter the course of disease, although relapses of chorioretinitis are still seen in treated children (Labadie and Hazemann, 1984; McAuley et al., 1994). Severe congenital toxoplasmosis must be distinguished from infection with rubella, CMV, herpes simplex and syphilis.

Immune-compromised hosts with T cell defects, such as patients with hematologic malignancies (especially Hodgkin's disease and other lymphomas), organ transplant recipients, AIDS patients and patients receiving immunosuppressive therapy with corticosteroids and cytotoxic drugs may have encephalitis, pneumonitis and myocarditis as manifestations of toxoplasmosis. These infections are usually fatal if not recognized and treated. While toxoplasmosis in these patients usually is a consequence of the recrudescence of a latent infection acquired before immune suppression occurred, it may also occur due to recently acquired acute infection with the parasite. *Toxoplasma gondii* can be transmitted by a transplanted organ resulting in acute toxoplasmosis in the recipient. The incidence of toxoplasmosis due to various organ transplants is currently unknown; as there is no registry for these cases. Trimethoprim-sulfamethoxazole or pyrimethamine can be used as prophylaxis against toxoplasmosis in organ transplantation. A review of cardiac transplants at Stanford Medical Center from 1980 to 1996 (Montoya et al., 2001), demonstrated that of 575 donor-recipient pairs 32 transplants were done in which the donor was serologically positive for *T. gondii* and the recipient was negative. Of these 32 patients, 16 received prophylaxis and none of these 16 patients developed toxoplasmosis. In contrast four of the remaining 16 patients without prophylaxis developed fatal toxoplasmosis. Toxoplasmosis has also been reported following renal transplantation (Renoult et al., 1997), liver transplantation and allogeneic bone marrow transplantation where fever, encephalitis and pneumonia were the main clinical features occurring within the first 3 months post-transplantation. Chorioretinitis has also been reported following transplantation and may be the result of reactivation of latent infection in the host or disseminated infection in a seronegative recipient. Toxoplasmosis occurred in 0.97% of 4,231 allogeneic transplants, most likely due to the use of trimethoprim-sulfamethoxazole prophylaxis after engraftment in these patients in the majority of institutions (Martino et al., 2000). In bone marrow transplant, toxoplasmosis frequently involves the lung and is associated with a mortality rate of >90%.

In the setting of HIV infection the most common clinical manifestation of toxoplasmosis is encephalitis (Luft and Remington, 1992), which occurs when the CD4+ cell count is below 200 cells/ μ L. With immune reconstruction due to active antiretroviral therapy the incidence of toxoplasmosis has fallen dramatically in HIV-infected patients. Encephalitis is due to the reactivation of latent infection. Clinical findings include altered mental state, seizures, weakness, cranial nerve disturbances, sensory abnormalities, cerebellar signs, meningismus, movement disorders and neuropsychiatric manifestations. The most common presentation seen in about 75% of cases is the sub-acute onset of focal neurologic abnormalities such as hemiparesis, personality changes or aphasia. Spinal cord involvement can occur and manifests as motor or sensory disturbances of single or multiple limbs, bladder or bowel dysfunctions or both, and local pain (Mehren et al., 1988; Herskovits et al., 1989). Acute acquired infection in the setting of AIDS has been reported to present with multiorgan involvement often manifesting with acute respiratory failure and hemodynamic abnormalities similar to septic shock (Oksenhendler et al., 1990). Pneumonia due to toxoplasmosis, prior to active retroviral therapy, was reported in up to 5% of advanced cases of AIDS (Derouin et al., 1990) with a mortality rate of 35%. Extrapulmonary disease was present in about 50% of cases with toxoplasmic pneumonitis (Oksenhendler et al., 1990). Gastrointestinal involvement may result in abdominal pain, ascites (due to involvement of the stomach, peritoneum or pancreas), diarrhea and hepatic failure. Uncommon manifestations of toxoplasmosis in AIDS patients include chorioretinitis (Holland et al., 1988), panhypopituitarism, diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion, orchitis and myositis (Gheradi et al., 1992).

3. History of clinical observations on *T. gondii*

It was about 25 years from the initial reports of possible toxoplasmosis in humans until *T. gondii* was clearly established as a human pathogen. Castellani (1914) was probably the first

to describe a *T. gondii*-like parasite in smears of the blood and spleen from a 14 year old boy from Ceylon who died from a disease characterized by severe anemia, fever and splenomegaly. Fedorovitch (1916) observed organisms similar to those reported by Castellani in the blood of a 10 year old boy from a region of the Black Sea who also had anemia, fever and splenomegaly. Chalmers and Kamar (1920) reported similar organisms in a soldier in the Sudan who had chronic headache, fever and diarrhea. These cases, however, were incompletely studied and it is possible that these cases were *Leishmania* spp. In 1923, Janků reported on “an 11 month old child (V.P.), the son of a carriage driver... who was admitted to the Children’s Clinic of Professor Pešina suffering from enormous increasing hydrocephalus” (Janků, 1923). This child died and both the clinical description and autopsy results were presented by Janků. Review of this case clearly demonstrates that the child had severe congenital toxoplasmosis. On physical examination chorioretinitis was present “In the papilla, the center of the area just described, there was a rich black pigment which was combined with a grayish white shiny material of azure tone, and finely stranded, running horizontally to the nasal edge (indirect image) of the abnormal spot in the macular region, retinal veins were missing in the area of the lesion”. The illustrations which accompany this case demonstrate classic fundoscopic changes due to toxoplasmosis. On pathology several “sporocysts” were identified “Histological sections showed a number of sporocysts, dispersed around the entire pathological region... The parasite was most strongly stained with hematoxylin and eosin... The sporocysts typical shape was egglike, the rounded shape corresponding to a perpendicular section of the sporocyst.” No mention is made of free tachyzoites. The accompanying photomicrographs leave no doubt that these were tissue cysts of *T. gondii*. Despite this description, Janků did not identify this patient as having toxoplasmosis or the observed organism as *T. gondii*. The material from this case is thought to have been destroyed during World War II bombings so confirmation of these findings is not possible. Torres (1927) described a similar case in an infant from Brazil who died with convulsions at two days of age. Although Janků only referred to his organisms as Sporozoa and Torres as *Encephalitozoon chagasi*, Levaditi (1928) suggested that both cases were due to *T. gondii*. Coulon (1929) observed parasites, which he called *E. brumpti*, in the spinal fluid of a 17 year old boy from Corsica who died of meningitis. Wolf and Cowen (1937) described a parasite, which they called *E. hominis*, in the nervous system and retina of an infant with encephalitis, chorioretinitis and internal hydrocephalus. As pointed out by Sabin in 1937, this parasite was indistinguishable from *T. gondii* (as noted in Sabin, 1942). The cause of confusion in the identification of this organism in tissue was its slight difference in appearance in fixed histological specimens compared with smears from cultures or peritoneal fluid of experimentally infected animals.

In 1939 Wolf, Cowen, and Paige were the first to conclusively identify *T. gondii* as a cause of human disease (Wolf et al., 1939 a, b). The described patient was an infant girl who was delivered full-term by Caesarean section on May 23, 1938 at Babies Hospital, New York, USA. Following delivery, at 3 days of age this child developed seizures and chorioretinitis was present in both eyes. When the child died at 1 month of age an autopsy was performed, which demonstrated free and intracellular *T. gondii* in lesions of encephalomyelitis and retinitis. Samples of cerebral cortex and spinal cord were homogenized in saline and inoculated intracerebrally into rabbits and mice; and these animals developed encephalitis from which *T. gondii* was isolated. *Toxoplasma gondii* isolated from these animals was successfully passaged into other mice. Studies by Sabin demonstrated that this human strain was neither biologically nor immunologically different from isolates from other animals (i.e. guinea pig isolates). Wolf, Cowen and Page reviewed in detail their own cases and those reported by others, particularly Janků (1923) and Torres (1927) of *T. gondii*-like encephalomyelitis and chorioretinitis in infants (Wolf and Cowen, 1937, 1938; Wolf et al., 1939a, b, 1940; Cowen et al., 1942; Paige et al., 1942) and concluded that this was a recognizable syndrome due to human infection with *T. gondii*. In addition, a case reported by de Lange (1929), who found protozoa in sections of the brain of a 4 month old child born with hydrocephalus was also reviewed and re-examined

by Wolf and Cowen [reviewed by Sabin, 1942]) and identified as being due to *T. gondii*. In 1939 Sabin isolated *T. gondii* from two children, R.H. aged 6 years and W.B.D. aged 8 years, with encephalitis. These cases were reported in 1940 and 1941 (Sabin, 1941).

The 6 year old was described as “R. H., a white boy aged 6 years, who was born and raised in Cincinnati, was admitted to the Contagious Division of the Cincinnati General Hospital on October 31 1939, complaining chiefly of weakness of the legs and headache... The history of the present illness begins with an incident on October 22, 1939, when the boy received a blow on the head with a baseball bat... There was no evidence of injury to the head or even of localized tenderness... The positive physical signs outside of the nervous system consisted of (1) a generalized lymphadenopathy involving especially the anterior and posterior cervical nodes and to a lesser extent the axilla and inguinal nodes and (2) a palpable spleen. He died on the thirtieth day of the disease coincidentally with a rise in temperature to 108.4°F... The pathologic focus was apparent even under low magnification as a moth-eaten, necrotic and honeycombed area which was infiltrated with a varying number of cells which had irregular pyknotic nuclei... On the thirteenth day after inoculation [of nervous tissue from this case] one of the mice exhibited a swollen abdomen and puncture yielded a large amount of peritoneal exudate in which *Toxoplasma* organisms were found extracellularly and intracellularly.... Subinoculation of the tissues from the mice which showed *Toxoplasma* produced a fatal toxoplasmosis in each instance.” This laboratory strain, labeled RH, became the prototypical Type I strain and since 1938 has been passaged in mice in many laboratories. After this prolonged passage its pathogenicity for mice has been stabilized (Dubey, 1977) and it has lost the capacity to produce oocysts in cats (Frenkel et al., 1976).

In 1940 Pinkerton and Weinman reported finding *Toxoplasma* in the sections of tissues from a 22 year old man from Peru who died with concomitant *Bartonella* infection and fever (Pinkerton and Weinman, 1940). Pinkerton and Henderson (1941) reported on two adults (aged 40 and 50 years) with atypical pneumonia and a spotted fever like syndrome who died in St. Louis, Missouri, in whom they demonstrated *T. gondii* as the etiological agent, by finding the organism in tissue post-mortum and by serial passage in animals. These were the first reports of acute toxoplasmosis in adults without neurological signs.

Development of a serological test, the dye test, in 1948 by Albert Sabin and Harry Feldman was a major advance in the study of toxoplasmosis (Sabin and Feldman, 1948). This test is both sensitive and specific with no evidence for false results in humans. The ability to identify *T. gondii* infections based this serological test allowed epidemiological studies on the incidence of infection, demonstrating the widespread world-wide prevalence of this infection in humans. It also demonstrated that the clinical signs of clinical congenital toxoplasmosis occurred in other diseases and assisted in the differential diagnosis of congenital infections (Sabin and Feldman, 1949; Feldman and Miller, 1957).

Sabin in 1942 indicated that the contributions of Wolf, Cowen and Paige were the basis for the existing knowledge about congenital toxoplasmosis. Sabin proposed that the clinical signs of hydrocephalus or microcephalus, intracerebral calcification and chorioretinitis, could be used to define cases of congenital toxoplasmosis. These four signs helped to define the clinical epidemiology of this infection; however, it was subsequently realized that rubella, CMV, HSV and syphilis could produce similar congenital symptoms. Frenkel and Friedlander (1951) published a detailed account of five fatal cases of toxoplasmosis in infants that were born with hydrocephalus; *T. gondii* was isolated from two. They described the pathogenesis of internal hydrocephalus as a blockage of the aqueduct of Sylvius due to ventriculitis resulting from a *T. gondii* antigen-antibody reaction. This lesion is unique to human congenital toxoplasmosis and has never been verified in other animals (J.P. Dubey, unpublished data). This report was

the first in-depth description of lesions of congenital toxoplasmosis, not only in the CNS but also other organs. Sabin and Warren (1942) reported the effectiveness of sulfonamides against murine toxoplasmosis and Eyles and Coleman (1953) discovered the synergistic effect of combined therapy with sulfonamides and pyrimethamine; the latter is the standard therapy for toxoplasmosis in humans (Remington et al., 2001).

Hogan (1951) provided the first detailed clinical description of ocular toxoplasmosis. Siim (1956) published on the association of lymphadenopathy and acquired toxoplasmosis in adults. These findings were confirmed by Beverley and Beattie (1958) in a series of 30 patients. A more complete appreciation of the spectrum of symptoms associated with acute acquired toxoplasmosis was achieved with the report of outbreaks of acute toxoplasmosis in adults in the USA (Teutsch et al., 1979) and Canada (Bowie et al., 1997).

In the 1960s Georges Desmonts initiated studies in Paris, France looking at seroconversion in women during pregnancy and the transmission of *T. gondii* to the fetus. Prophylactic treatment was given to women who seroconverted during pregnancy. This 15 year study demonstrated that: (i) infection acquired during the first two trimesters was most damaging to the fetus; (ii) transmission depended on when women acquired infection during the pregnancy; (iii) those who were seropositive prior to pregnancy did not transmit infection to the fetus; and (iv) treatment with spiramycin reduced congenital transmission (Desmonts and Couvreur, 1974a, b). Thalhammer initiated a similar screening program for pregnant women in Austria (see Thalhammer, 1973) generating similar results. A similar program on neonatal serological screening and early treatment for congenital *T. gondii* infection was initiated in Massachusetts, USA in 1980s (Guerina et al., 1994). The Chicago Collaborative trial reported on the efficacy of the treatment of congenitally infected children (McAuley, 1994). Garin and Eyles (1958) found spiramycin to have antitoxoplasmic activity of in mice. Since spiramycin is non-toxic and does not cross placenta it has been used prophylactically in women during pregnancy to reduce transmission of the parasite from mother to fetus (Desmonts and Couvreur, 1974b). The optimal treatment of congenital infection is, however, not fully delineated, and many issues related to the benefit of screening and treatment in pregnancy still remain to be determined.

Remington et al. (1968) first suggested that the detection of IgM antibodies in cord blood or infant serum would be useful in the diagnosis of congenital toxoplasmosis since IgM antibodies do not cross the placenta, whereas IgG antibodies do. Remington (1969) modified the indirect fluorescent antibody test (IFAT) and the ELISA (Naot and Remington, 1980) to detect IgM in cord blood. Desmonts et al. (1981) developed a modification of IgM-ELISA, combining it with the agglutination test (IgM-ISAGA) to eliminate the necessity for an enzyme conjugate. Although IgM tests are not perfect, they have proved useful for screening programs (Remington et al., 2001). A simple direct agglutination test was initially developed by Fulton (1965) and improved by Desmonts and Remington (1980) and Dubey and Desmonts (1987) who called it the modified agglutination test (MAT). The MAT has been used extensively for the diagnosis of toxoplasmosis in animals. Burg et al. (1989) first reported detection of *T. gondii* DNA from a single tachyzoite by amplification of the B1 gene in a PCR. Several subsequent PCR tests have been developed using different gene targets. Overall, this technique has proven very useful in the diagnosis of clinical toxoplasmosis.

Before 1950, virtually all cases of ocular toxoplasmosis were considered to result from congenital transmission (Perkins, 1961). Rieger (1951) can be credited with the concept of post-natally acquired *T. gondii* as well as the theory that recurrence may be related to immunocompromised states. In 1952 Helenor Campbell Wilder Foerster, a technician in the registry of Ophthalmic Pathology at the Armed Forces Institute of Pathology, (AFIP), Washington, D.C. USA established a clear link between *T. gondii* and chorioretinitis (Holland et al., 2002). Wilder put enormous effort into the identification of microbes in “tuberculous” eyes

submitted to the AFIP, but never identified bacteria or spirochetes by special staining until she identified *T. gondii* in the retinas of these eyes. Data obtained with the Sabin-Feldman dye test had suggested the potential role of *T. gondii* as an unrecognized cause of ocular disease in adults. Vail (1943), Frenkel, (1949) and Rieger (1951) all described series of adult patients with chorioretinal lesions and positive *T. gondii* antibody tests. Wilder's case series of 53 eyes was the first clear histological evidence of the importance of *T. gondii* as a cause of chorioretinitis. This case series consisted of 53 eyes that had been enucleated due to pain and blindness. All of the eyes in this series had lesions that were granulomatous with central necrosis and *T. gondii* was consistently found in the necrotic areas. Wilder subsequently collaborated with Jacobs and Cook and found most of these patients with histologically confirmed *T. gondii* infection had low levels of dye test antibodies (a titer of 1:16) and in one patient antibodies were demonstrable only in undiluted serum (Jacobs et al., 1954a). As a result of this work, ocular toxoplasmosis resulting from congenital infection became accepted as the leading cause of posterior uveitis. This work also demonstrated that toxoplasmosis, not tuberculosis, was the etiology of these retinochoroidal lesions. Jacobs et al. (1954b) made the first isolation of *T. gondii* from an eye of a 30 year old male hospitalized at the Walter Reed Army Hospital, USA. The eye had been enucleated due to pain associated with elevated intraocular pressure.

Prior to Wilder's report, tuberculosis was routinely diagnosed as the etiology of these retinochoroidal lesions. Post-natally acquired infection with ocular involvement, as well as ocular manifestations of congenital disease, were fully characterized by Hogan (1958). It was further noted by Hogan that ocular symptoms of toxoplasmosis occur largely in the presence of systemic symptoms (Hogan et al., 1964); however it is now appreciated that ocular disease can occur in isolation. The idea, now known to be incorrect, that almost all toxoplasmic chorioretinitis is congenital was supported by a publication from Perkins (1973) on congenital infection. Episodes of chorioretinitis in children and adults were attributed to congenital infection that went undetected at birth (Hogan, 1961). More recent studies have refuted these earlier assumptions. It is now appreciated that ocular disease is often the only manifestation of recent, post-natally acquired infection (Ongkosuwito et al., 1999). Ophthalmologists from southern Brazil initially discovered ocular toxoplasmosis in siblings and subsequently noted that among patients with post-natally acquired toxoplasmosis who did not have retinochoroidal scars before, 8.3% developed retinal lesions during a 7 year follow-up (Silveira et al., 1987, 1988, 2001). Ocular toxoplasmosis was diagnosed in 20 of 95 patients with acute toxoplasmosis associated with the Canadian waterborne outbreak of toxoplasmosis in 1995 (Burnett et al., 1998; also see Holland, 2003). Also, retinal lesions have been known to develop long after initial infection (Silveira et al., 2001). It has been suggested that in some geographic areas acquired infection may account for the majority of cases of ocular toxoplasmosis (Holland, 1999; Gilbert and Stanford, 2000).

Treatment of ocular toxoplasmosis with antimicrobial drugs began in the early 1950s. In 1953, Eyles and Coleman demonstrated the use of pyrimethamine and sulfonamides (Eyles, 1953), which remains the gold standard for anti-Toxoplasma therapy. Hogan (1958) demonstrated that this treatment resulted in resolution of chorioretinitis in adults. Currently, drug therapy for ocular toxoplasmosis is usually administered only if there is reactivation of the infection as current drugs have no effect on latent forms of this parasite. The most common regimen used in the 1991 survey of experts in the treatment of uveitis was pyrimethamine, sulfadiazine, prednisone and folic acid in 32% of respondents and an additional 27% added clindamycin to this regimen (Engstrom et al., 1991).

Encephalitis due to *T. gondii* in immuno-compromised patients was first reported from patients with Hodgkin's disease during immunosuppressive treatment (Flament-Durand et al. 1967). It was, however, a rarely seen infection before the emergence of AIDS in adults in the 1980s.

Luft and Remington (1983) reported a series of patients with encephalitis due to *T. gondii* that was fatal if not treated. This infection occurred as a result of reactivation of chronic infection related to the defect in T cell immunity induced by HIV infection. This infection was one of the most common neurological complications of AIDS prior to the advent of active antiretroviral therapy. With immune reconstitution this infection is not seen; however it is still a problem in areas where HIV treatment is not available.

4. Summary

Toxoplasma gondii was discovered 100 years ago. Its identification was rapidly followed by the recognition that it was a human pathogen. During the past 100 years the spectrum of diseases caused by this ubiquitous pathogen has expanded to include both congenital and acute infections as well as the recognition of the diseases caused by this pathogen in the immune-compromised host. Recent data on behavioral changes in animals due to chronic toxoplasmosis is leading to research on the effect of this pathogen on the behavior of humans. Experimental studies on *T. gondii* have resulted in its becoming a model organism for studies on host pathogen interactions. Integration of the clinical and experimental data on *T. gondii* should continue to lead to important insights into how pathogens evolve into successful parasites.

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