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Severe neurological and ocular manifestations in paediatric patients with toxoplasmosis. Case-series study with review of the current literature

Ciężkie manifestacje neurologiczne i okulistyczne wrodzonej toksoplazmozy u pacjentów pediatrycznych. Opis przypadków wraz z przeglądem aktualnej literatury

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Abstract

Toxoplasmosis, both congenital and postnatally acquired, is a parasitic disease caused by infection with the protozoan *Toxoplasma gondii*. The most serious manifestation of this disease is congenital toxoplasmosis, resulting from transplacental infection of the foetus during pregnancy. Retinochoroiditis, intracranial calcifications, and hydrocephalus are considered the classic triad of congenital toxoplasmosis. This article describes four cases of severe neurologic and ocular manifestations in paediatric patients diagnosed with toxoplasmosis. The main aim was to examine the nature of clinical presentation as well as to emphasise the necessity of properly administered antiparasitic therapy and underline the importance of prenatal screening to reduce the risk of congenital transmission to the foetus.

Keywords: paediatric toxoplasmosis, congenital toxoplasmosis, *Toxoplasma gondii*, ocular toxoplasmosis

Streszczenie

Toksoplazmoza, zarówno wrodzona, jak i nabyta, jest chorobą pasożytniczą wywołaną zakażeniem pierwotniakiem *Toxoplasma gondii*. Najpoważniejszą postacią tej jednostki chorobowej jest toksoplazmoza wrodzona, wynikająca z zakażenia płodu drogą przezłożyskową w czasie trwania ciąży. Zapalenie siatkówki i naczyńówki, zwapnienia śródczaszkowe oraz wodogłowie są uważane za klasyczną triadę toksoplazmozy wrodzonej, zwaną również triadą Sabina–Pinkertona. W niniejszym artykule przedstawiono serię czterech przypadków ciężkich manifestacji klinicznych – neurologicznych i okulistycznych u pacjentów pediatrycznych ze zdiagnozowaną toksoplazmozą wrodzoną. Istotą pracy było zwięzłe scharakteryzowanie obrazu klinicznego toksoplazmozy wrodzonej, podkreślenie konieczności właściwie prowadzonej terapii przeciwpasożytniczej i znaczenia diagnostyki prenatalnej w redukcji ilości zachorowań na tę jednostkę chorobową.

Słowa kluczowe: toksoplazmoza u dzieci, toksoplazmoza wrodzona, *Toxoplasma gondii*, toksoplazmoza oczna

INTRODUCTION

Toxoplasmosis, caused by infection with the widely distributed protozoan parasite *Toxoplasma gondii*, is a very common disease worldwide⁽¹⁻³⁾. The clinical course of toxoplasmosis may vary from asymptomatic to life-threatening forms, especially in immunocompromised patients⁽⁴⁾. Infection with *Toxoplasma gondii* in humans may occur by consumption of raw or undercooked meat contaminated with tissue cysts⁽⁵⁾ as well as food or water contaminated with cat faeces or during blood transfusion⁽⁶⁾ or organ transplantation⁽⁷⁾. It is also widely known that an infection acquired during or shortly before pregnancy may be transmitted transplacentally (vertically) and cause severe abnormalities to the developing foetus⁽⁸⁾. Although retinochoroiditis, intracranial calcifications, and hydrocephalus are considered the classic triad of congenital toxoplasmosis, the manifestations may also include microcephaly, epilepsy, psychomotor and mental retardation, hepatosplenomegaly, petechiae due to thrombocytopenia, and anaemia⁽⁹⁾. However, the most devastating possible consequences of primary maternal infection include spontaneous abortion, intrauterine growth restriction or even intrauterine foetal death^(10,11). It is estimated that approximately 90% of pregnant women primarily infected with *Toxoplasma gondii* during gestation remain asymptomatic, and most children born with congenital toxoplasmosis do not initially present any symptoms⁽¹²⁾ which makes the speculative diagnosis difficult. The above mentioned retinochoroiditis, which may appear as a result of both congenital and acquired infection, may lead to serious vision-threatening complications such as retinal detachment, choroidal neovascularisation, and glaucoma. This paper aims to present four cases of severe ocular and neurologic manifestations of toxoplasmosis in paediatric patients admitted to the Department of Paediatric Infectious Diseases, Medical University of Lodz, Poland (regional reference centre for paediatric infectious diseases). This case study seeks to examine the nature of clinical presentation of toxoplasmosis in paediatric patients.

CASE 1

An 11-year-old girl was admitted to the infectious diseases department with a suspected diagnosis of ocular toxoplasmosis. She was born at 39 weeks of gestation without any maternal or newborn complications. No data regarding toxoplasmosis during pregnancy or serological tests was found. According to the parents, the patient's development proceeded normally, without any developmental delay or disorders. The parents reported recurrent herpes simplex labialis and upper respiratory tract infections, as well as abdominal and knee pain that had been appearing periodically for the preceding two years. The patient had stayed under the care of an ophthalmological outpatient

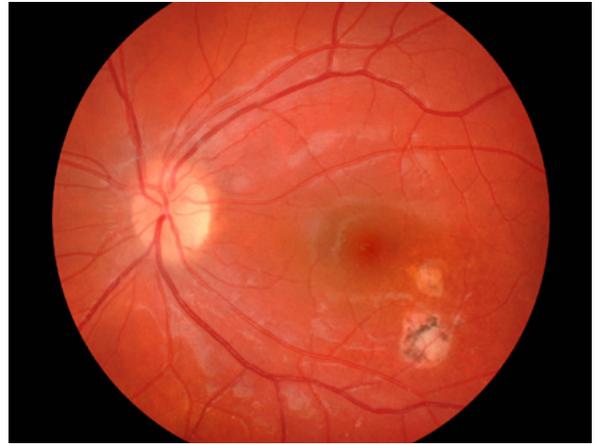


Fig. 1. Fundus photograph of whitish foci of retinochoroiditis and pigmented scar in the right eye (case 1)

clinic for four years due to refractive error corrected with spectacles, but no funduscopy was ever performed during the examination.

Shortly before the above-described hospitalisation the girl was presented to the emergency department with acute severe headache. Neurological and laryngological consultations showed no abnormalities. However, the fundoscopic examination performed during an ophthalmologist evaluation revealed bilateral pigmented chorioretinal scars (shown in Fig. 1).

Serological tests were performed and showed *Toxoplasma* IgG 108.4 IU/mL (negative results <7.2 IU/mL, positive results >8.8 IU/mL) and negative *Toxoplasma* IgM result. During the hospitalisation, serological tests showed *Toxoplasma* IgG level of 121.0 IU/mL together with high *Toxoplasma* IgG avidity (>0.9), *Borrelia* IgM 22.2 AU/mL (negative results <18.0 AU/mL, positive results >22.0 AU/mL). Tests for *Borrelia* IgG, CMV IgG and IgM, *Toxoplasma* IgA and IgM were negative. At the same time, the ophthalmologist evaluation revealed an atrophic pigmented chorioretinal scar with a size of one disc diameter in the left eye and extensive postinflammatory pigmented chorioretinal scar with a size of three-disc diameters in the right eye. The diagnosis of bilateral ocular toxoplasmosis was confirmed, and antiparasitic treatment with pyrimethamine (37.5 mg per day) and sulfadiazine (1,000 mg four times a day) together with folic acid (15 mg twice a week) was initiated.

During the hospital follow-up appointment held three weeks later, the patient did not present any side effects associated with the antiparasitic treatment, so the therapy was continued. However, one month later the drug doses were reduced due to leukopenia and neutropenia. From that time, the therapy consisted of pyrimethamine (25 mg per day), sulfadiazine (1,000 mg three times a day), and folic acid (15 mg twice a week). The initial antiparasitic treatment was completed after seven months since there was no evidence of active inflammation.

The first recurrence was found two months after the end of previous treatment. Ophthalmological evaluation

revealed an active inflammation in the left eye, although the patient did not report any visual disturbances. The antiparasitic therapy consisting of pyrimethamine (25 mg per day), sulfadiazine (1,000 mg three times a day), and folic acid (15 mg twice a week) was reintroduced. From that time, the patient stayed under the care of an ophthalmological outpatient clinic and underwent follow-up examinations.

Within two years after the end of previous treatment another recurrence was identified. The patient complained of periodically appearing visual disturbances (scotomas) in the left eye. Funduscopic examination revealed an active inflammation together with vitreous haze in the left eye. Because of clinical symptoms and the results of the ophthalmological examination and serological tests (*Toxoplasma* IgG level 67.5 IU/mL), a decision was made to reimplement the therapy consisting of pyrimethamine (25 mg twice a day), sulfadiazine (1,000 mg four times a day), and folic acid (15 mg three times a week), together with a corticosteroid – methylprednisolone (16 mg per day with a reduction by 4 mg every week), as suggested by an ophthalmologist.

During the next hospital follow-up appointment, the patient's general condition was good. Funduscopic examination revealed a postinflammatory chorioretinal scar in the left eye and no signs of active inflammation in the right eye. The antiparasitic treatment was continued.

CASE 2

A 2-year-old boy with congenital toxoplasmosis was admitted to the Paediatric Infectious Disease Unit. No data regarding toxoplasmosis during pregnancy or serological tests was found. The recommended first-line treatment based on pyrimethamine, sulfadiazine and folic acid was initiated on the ninth day after birth. An enlargement of cerebral ventricles due to hydrocephalus and separated cranial sutures were diagnosed. Serological tests showed *Toxoplasma* IgG >400 IU/mL and negative *Toxoplasma* IgA and IgM results. Correct antiparasitic treatment was continued with increased drug doses. From that moment, the therapy consisted of sulfadiazine (170 mg twice a day), pyrimethamine (3.5 mg per day), and folic acid (3 mg three times a week).

One month later, during the next hospitalisation, brain magnetic resonance imaging (MRI) showed signs of brain tissue degeneration. At the same time, funduscopy revealed an active inflammatory focus in the left eye, which is shown in Fig. 2. Fluorescent angiogram obtained from the patient is shown in Fig. 3. The patient was also diagnosed with hypochromic anaemia. Levels of *Toxoplasma* IgG antibodies were significantly elevated (IgG 319.0 IU/mL). The treatment was modified again and consisted of sulfadiazine (240 mg twice a day), pyrimethamine (5 mg per day), and folic acid (5 mg two times a week).

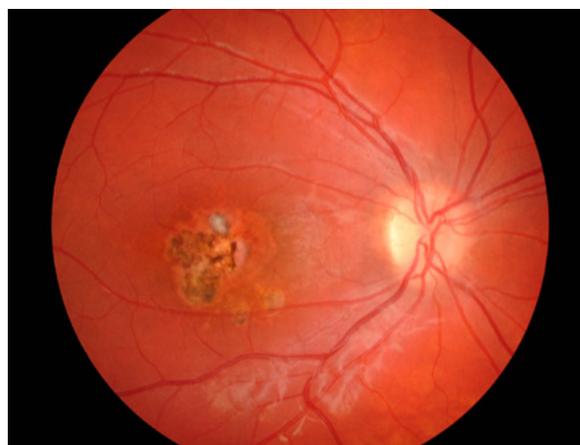


Fig. 2. Active lesions seen as whitish foci of retinochoroiditis in the left eye (case 2)

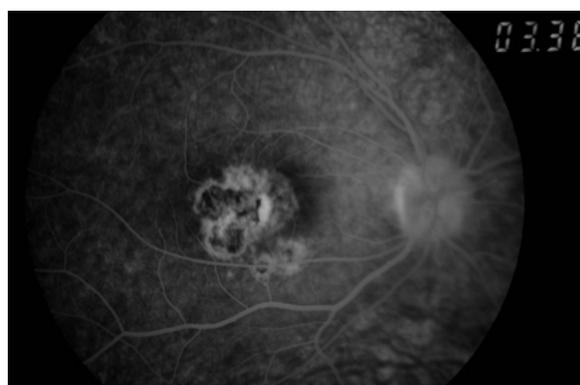


Fig. 3. Fluorescent angiogram of ocular toxoplasmosis (case 2)

Two months later, following progression of symptoms, the patient was referred for a neurosurgical procedure. At that time, *Toxoplasma* IgG antibodies were increased (IgG 185 IU/mL). A decision was made to increase the drug doses. The modified therapy consisted of sulfadiazine (320 mg twice a day), pyrimethamine (6 mg per day), and folic acid (5 mg twice a week). A few days later, the patient was admitted to the Neurosurgical Department, where a ventriculoperitoneal shunt equipped with a Rickham reservoir (also known as Ommaya reservoir) was implanted. Two months following the surgery, the patient was readmitted in order to perform a clinical post-operation review. Due to persistently high levels of *Toxoplasma* IgG (110 IU/mL), a decision was made to once again increase the drug doses, so that the therapy consisted of sulfadiazine (350 mg twice a day), pyrimethamine (7 mg per day), and folic acid (5 mg three times a week).

Even though the levels of *Toxoplasma* IgG antibodies were found to be significantly lower during the next two hospitalisations, a decision was made to further increase the doses of administered drugs to prevent any complications.

After nearly 12 months of treatment, the patient's condition appeared to have stabilised. The examination showed no new abnormalities. No active inflammatory foci were found during the funduscopic examination.

CASE 3

An 18-month-old boy with congenital toxoplasmosis was first admitted to the Paediatric Infectious Disease Unit after being diagnosed with bilateral retinochoroiditis, hydrocephalus, and microcephaly. MRI scans of the brain are shown in Figs. 4 and 5. Therapy consisting of pyrimethamine, sulfadiazine and folinic acid was administered just after birth. Due to the high probability of foetal infection, the patient's mother had been treated with spiramycin since the 20th week of pregnancy. One week prior to hospitalisation, the patient underwent a ventriculoperitoneal shunt implantation procedure. During the hospitalisation, the patient suffered an episode of loss of appetite and elevated



Fig. 4. Magnetic resonance imaging (MRI) scan of the brain (case 3)

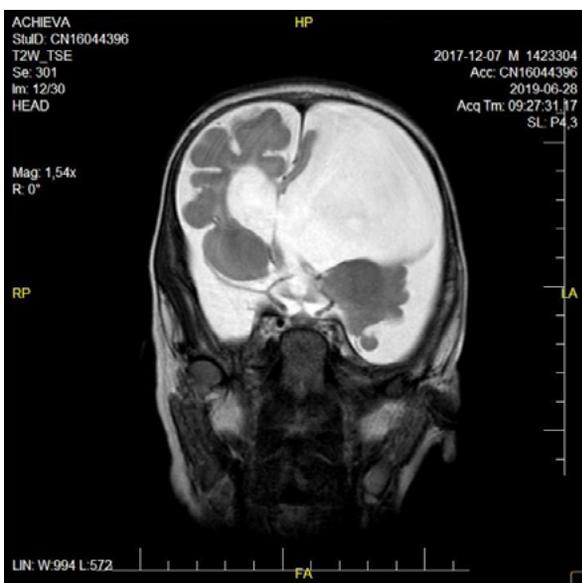


Fig. 5. Magnetic resonance imaging (MRI) scan of the brain (case 3)

body temperature (37.9°C). Laboratory liver function tests revealed an elevated alanine aminotransferase (ALT) level (95 U/L). The patient was negative for rotavirus, adenovirus or norovirus infection. The stool culture was negative for both *Salmonella* and *Shigella* species.

Due to the persistently elevated levels of *Toxoplasma* IgG, antiparasitic therapy consisting in sulfadiazine (280 mg twice a day), pyrimethamine (6 mg per day), and folinic acid (5 mg per day) was continued without introducing any additional treatment.

During the hospital follow-up appointment held six months later to evaluate any side effects associated with the treatment, the level of *Toxoplasma* IgG was found to be within the normal range. No active inflammatory foci were found during fundoscopic examination. A decision was made to increase both drug doses as well as the frequency of administration of sulfadiazine (350 mg twice a day) pyrimethamine (7 mg per day), and folinic acid (5 mg three times a week).

On the day of hospital discharge, the patient was asymptomatic. The examination showed no abnormalities and no evidence of recurrence of retinochoroiditis.

CASE 4

An 8-year-old boy complaining of decreased visual acuity for two months was admitted to the Paediatric Infectious Disease Unit with a diagnosis of ocular toxoplasmosis (bilateral retinochoroiditis) and primal therapy with prednisone and spiramycin for the purpose of modifying the treatment. The boy was born at 42 weeks of gestation. The newborn was at risk for birth asphyxia. No data regarding toxoplasmosis during pregnancy or serological tests was found. One month before the admission, the patient was presented to the paediatric ophthalmology department in another hospital. Serological tests were performed and showed *Toxoplasma* IgG 373.0 IU/mL (negative results <7.2 IU/mL, positive results >8.8 IU/mL), high *Toxoplasma* IgG avidity, and negative *Toxoplasma* IgM result. Bilateral retinochoroiditis was detected during the fundoscopic examination performed during an ophthalmologist evaluation.

During the hospitalisation, the patient complained of blurry vision in the right eye. Ophthalmologist evaluation revealed an active focus of infection appearing as a cotton-wool spot together with vitreous haze in the right eye and pigmented chorioretinal scar in the left eye. Serological tests showed *Toxoplasma* IgG level – 313.0 IU/mL (negative results <7.2 IU/mL, positive results >8.8 IU/mL). Tests for *Toxoplasma* IgA and IgM were negative. Optical coherence tomography (OCT) examination revealed an active inflammatory lesion in the retina of the right eye. Antiparasitic treatment with pyrimethamine (25 mg a day) and sulfadiazine (500 mg three times a day) together with folinic acid (25 mg three times a week) was initiated. The corticosteroid therapy was continued, but with a necessary gradual dose reduction.

In the course of the last follow-up appointment, the patient presented a good general condition. The *Toxoplasma* IgG level was lower compared to the last hospitalisation. Funduscopic examination also showed an improvement compared to the previous one. Therefore, the six-month antiparasitic therapy was discontinued. The patient has remained under the care of an ophthalmological outpatient clinic.

DISCUSSION

In this paper, we aimed to present a diverse and severe course of congenital toxoplasmosis in four children in Poland, which is a country with a fully established screening programme for congenital toxoplasmosis.

Despite the well-known and accepted algorithm for the serodiagnosis of toxoplasmosis in pregnant women, when analysing the four cases described in our study, it turned out that mother's infection status was unknown in three of them.

Numerous factors contribute to the occurrence of this situation. It is highly probable that most of these women were not aware of their pregnancy early enough to undergo serodiagnosis for toxoplasmosis. Furthermore, expectant mothers may lack sufficient awareness regarding disease prevention and the importance of undergoing multiple tests for toxoplasmosis throughout their pregnancy. Additionally, the issue predominantly affects women with lower social status, making it more challenging for them to fully comprehend the necessity of these tests and engage in discussions with gynaecology and obstetrics specialists.

In a 2021 research paper by Mueller et al., an analysis of 44 female patients was conducted, all of whom had children diagnosed with congenital toxoplasmosis⁽¹³⁾. The study revealed that despite the existence of national recommendations, several opportunities were overlooked to prevent congenital toxoplasmosis during the antenatal period and to diagnose and treat this condition in the neonatal period. The authors were not able to retrospectively ascertain the reasons for not treating these pregnant women, but they theorised that a lack of comprehension regarding the significance of serology results might have contributed to this situation. Furthermore, even when treatment was initiated, it was rarely sufficient, both due to delayed initiation and the ineffectiveness of the prescribed drugs in foetal treatment⁽¹³⁾.

Multiple published studies^(14–16) have emphasised the importance of serologic screening for maternal *Toxoplasma* infections in pregnancy. This is due to the fact that this infection, when congenital, can cause serious neurological and ocular complications and, in some cases, even spontaneous abortion or intrauterine foetal death. It is, however, completely treatable *in utero* (when found early enough).

According to the regulations regarding new standards in perinatal care set out on 16 August 2018, by the Polish Minister for Health, the first gestational screening for

Toxoplasma IgG and IgM antibodies should be performed no later than at 10 weeks of pregnancy (except in cases where the presence of *Toxoplasma* IgG antibodies is discovered before pregnancy) and again between the 21 and 26 weeks of gestation, in women who have shown a negative result for *Toxoplasma* IgG antibodies in the first trimester. It is believed that the implementation of the above-mentioned standards may improve the quality of perinatal care in Poland. However, as reported by the National Institute of Public Health NIH – National Research Institute – Department of Epidemiology and Surveillance of Infectious Diseases in the report entitled “Infectious diseases and poisonings in Poland”, the yearly occurrence of congenital toxoplasmosis varied between nine and 30 new cases, with an average of approximately 17.87 cases between 2015 and 2022, and there have been no alterations in occurrence subsequent to the implementation of the guidelines (with an average of 17.33 cases per year).

We have also found evidence of benefits of early screening for toxoplasmosis in Austria. As demonstrated by the Austrian National Programme, prenatal screening and treatment have resulted in substantial cost savings, both from the conventional societal perspective and from a budgetary point of view. Prusa et al. showed the positive economic value of preventive measures⁽¹⁷⁾. Additionally, implementing such procedures offers the opportunity to start treatment as early as possible, thereby reducing possible complications. One publication from 1990 showed that about 50% of pregnant women who acquire the infection during gestation without starting any treatment, will give birth to infected infants⁽¹⁸⁾.

In the broad update on congenital toxoplasmosis in humans worldwide by Dubey et al., through analysing previously published studies, the authors highlighted the role of education (instructions given in antenatal clinics and by obstetricians and midwives dealing with individual patients) in reducing the incidence of *Toxoplasma gondii* infections during pregnancy, as in France⁽¹⁹⁾.

On the other hand, authors from Canada suggested that routine screening for toxoplasmosis was not recommended in the Canadian population. This point of view was argued due to the low prevalence of the disease in this particular population and the therapeutic limitations that restrict the effectiveness of screening strategies⁽²⁰⁾.

It is worth noting that two patients from our study were diagnosed with ocular toxoplasmosis at school age (8 and 11 years old). While analysing the above-mentioned cases, we found it problematic to distinguish whether the ocular symptoms were caused by a postnatal infection or were late manifestations of congenital toxoplasmosis. The study by Gilbert and Stanford published in “British Journal of Ophthalmology”⁽²¹⁾ indicates that postnatal infection seems to be a more common cause of ocular toxoplasmosis. Thus, the diagnosis of ocular toxoplasmosis associated with foeto-maternal transmission of *Toxoplasma gondii* should be supported with both clinical and serological evidence⁽²²⁾.

Another crucial issue is correct treatment, which should start from the time of diagnosis and continue without any interruptions. The combination of pyrimethamine and sulfadiazine is regarded as the most efficient and widely used treatment for toxoplasmosis^(23–26). Due to the fact that pyrimethamine is a folic acid antagonist which can cause dose-related suppression of the bone marrow, folic acid supplements to pyrimethamine and sulfadiazine prevent anaemia which can arise during treatment.

Questions have been raised about corticosteroids given in combination with antiparasitic drugs to reduce the inflammatory reaction during active chorioretinitis. One of the published studies⁽²⁷⁾ suggested that therapy with pyrimethamine and sulfadiazine with the addition of corticosteroids (systemic or topical) could give satisfying outcomes, but further research is required to determine the beneficial effects of such treatment. On the other hand, Stanford and Gilbert suggested that using corticosteroids might not be safe for patients with ocular toxoplasmosis⁽²⁸⁾. Multiple studies have demonstrated that using corticosteroids alone can negatively impact the progression of toxoplasmosis.

Ocular toxoplasmosis is a progressive and recurring disease with vision-threatening complications and may, therefore, lead to serious visual impairment. For this reason, an infection with *Toxoplasma gondii* should be considered as a possible aetiology of retinochoroiditis in children. Although the analysis of the above reported cases suggests that despite antiparasitic treatment the recurrences of retinochoroiditis may be expected, proper therapy reduces both the progression of the symptoms and the risk of serious complications, such as vision loss.

After analysis of these four cases, we conclude that despite numerous studies and prenatal care programmes, the diagnosis and therapy of toxoplasmosis in children still remains controversial and challenging.

In our opinion, despite the medical expertise available, including screening guidelines and diligent care provided by physicians, there remain deficiencies in patient awareness of the disease in the newborns, and methods of treatment or transmission of the disease from the mother to the foetus.

CONCLUSIONS

In conclusion, we showed that the clinical presentation of toxoplasmosis in paediatric patients could be severe and cause serious complications. However, implementing and conducting an adequate therapy without interruptions may reduce the progression of symptoms. Thus, we strongly support the need for a pregnancy screening programme in Poland. It should be noted that awareness within the population with regard to this infection is crucial for its prevention. Prenatal screening allows the identification of women in whom foetal infection has been confirmed or is highly suspected and who, hence, should be started on antiparasitic treatment during pregnancy. This would help reduce

the risk of foetomaternal transmission of *Toxoplasma gondii* and allow the therapy of the newborn to be implemented as soon as possible.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: KM, AJO, AK, EMS. Collection, recording and/or compilation of data: KM, AJO, AK. Analysis and interpretation of data: KM, AJO. Writing of manuscript: KM, AJO. Critical review of manuscript: KZ, MT. Final approval of manuscript: EMS, KZ, MT.

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