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Congenital toxoplasmosis: potential outcomes and therapeutic challenges - a complex case report of the newborn with treatment-resistant manifestations

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ABSTRACT

Introduction and purpose

Toxoplasmosis, a prevalent parasitic infection caused by Toxoplasma gondii, impacts approximately one-third of the global population. Among congenital infections, Congenital Toxoplasmosis (CT) ranks second only to CMV infection in neonates. The severity of fetal and neonatal clinical manifestations depends on factors such as gestational age during infection, parasite load, infectious strain virulence, and maternal immune status. The organogenesis stage in the second trimester is identified as the critical period (10th-24th gestational weeks). Fetal CT may present with ultrasound-detected abnormalities, including intracranial calcifications, microcephaly, hydrocephalus, ascites, hepatosplenomegaly or severe intrauterine growth restriction. Even in the absence of symptoms at birth, CT can lead to long-term consequences such as hydrocephalus, seizures, and cognitive, auditory, and visual impairments.

The aim of this study is to present a clinical case of a patient with CT infection complicated by treatment-resistant hydrocephalus and neurological symptoms, including muscle tone disturbances and seizures.

Conclusion

The significance of screening tests cannot be overstated, as early intervention is crucial to prevent enduring complications. Routine counseling for pregnant women is imperative to raise awareness about Toxoplasma gondii infection, empowering them to adopt necessary preventive measures. Additionally, further research is warranted to assess the efficacy of diverse treatment protocols, the risk of adverse effects, and the effectiveness of emerging therapeutic agents.

Key words: congenital toxoplasmosis, toxoplasma gondii, hydrocephalus, seizures

INTRODUCTION

Toxoplasma gondii

Toxoplasmosis is a parasitic infection affecting both humans and animals, caused by the intracellular parasite Toxoplasma gondii. It is regarded as the most widespread parasitic infection worldwide, affecting up to one-third of the global population, as evidenced by various studies. [1;2;14] In immunocompetent individuals, infection typically proceeds asymptomatically. For those with weakened immune systems, it may manifest as a self-limiting disease with mild infection symptoms. In the case of immunosuppressed individuals, such as those with HIV, or in neonates, toxoplasmosis infection can have a severe course, leading to significant complications and long-term consequences. [3]

The definitive host of the protozoan parasite Toxoplasma gondii is the cat, in which oocysts develop within the gastrointestinal tract and are subsequently excreted in the animal's feces. Intermediate hosts include humans, sheep, cattle, pigs, birds, and mice. [3;15] Infection with T. gondii oocysts occurs through the ingestion of raw or undercooked meat, contact with cat feces, as well as the consumption of unfiltered water or unpasteurized goat's milk. Additionally, other sources of exposure include lakes, water reservoirs, and contaminated soil. [4;17;18]

Congenital Toxoplasmosis (CT)

Congenital toxoplasmosis (CT) stands as the second most common congenital infection in neonates after CMV infection. In the United States, the incidence of congenital toxoplasmosis among live-born neonates ranges from 1:3000 to 1:10000. [3;15] Following entry into the intermediate host's body, the parasite induces parasitemia lasting approximately 10 days. In individuals with intact immune systems, oocysts typically transition to a dormant form (bradyzoites) during this time, often without clinical manifestations. [4] However, it is during the parasitemic stage that the parasite can cross the placenta and lead to the development of congenital toxoplasmosis. [1;3] Congenital toxoplasmosis generally occurs through the transplacental transfer of infection acquired during pregnancy. Nevertheless, fetal infection can also be possible when there is

reactivation of latent infection in women with compromised immunity, such as due to immunosuppressive treatment or AIDS. [4;6;20]

The severity of clinical symptoms in the fetus and newborn depends on the gestational age at which the infection occurred, the parasite load, virulence of the infectious strain, and the maternal immune status. As pregnancy progresses, the placenta develops, thus increasing the risk of infection in parallel with the duration of pregnancy. [16;17] Studies indicate that the risk of fetal infection is approximately 2.2%, 23%, and 56% in the 6th, 18th, and 30th week of pregnancy, respectively. [5;6] In cases of intrauterine infection during the first trimester, it can lead to miscarriage or fetal demise. Researchers estimate the overall rate of fetal loss due to toxoplasmosis to range from 5% to 21%. [2] The critical period is the organogenesis stage in the second trimester of pregnancy (10th-24th gestational weeks), as fetal toxoplasmosis infection during this period contributes to severe postnatal impairments. Conversely, infection in the third trimester typically proceeds without clinical symptoms in 90% of cases. [7]

CT in fetuses may manifest through ultrasound findings such as intracranial calcifications, microcephaly, hydrocephalus, ascites, hepatosplenomegaly, or severe intrauterine growth restriction. [1;2] Inflammatory chorioretinopathy remains the most frequent clinical manifestation of congenital toxoplasmosis. [8;11] Even in the absence of symptoms at birth, children with CT can develop significant long-term consequences, including hydrocephalus, seizures, and cognitive, auditory, and visual impairments. [2;8]

We present a clinical case of a patient with congenital Toxoplasma gondii infection complicated by treatment-resistant hydrocephalus and neurological symptoms, including muscle tone disturbances and seizures.

CASE REPORT

The case involves a male neonate born during the 37th week of gestation via cesarean section due to fetal hydrocephalus. The pregnancy was complicated by hypothyroidism and toxoplasmosis, which had been treated with Rovamycine (Spiramycinum) since the 16th week of pregnancy. The newborn had a birth weight of 3430g and a head circumference of 36cm (90-97th percentile), evaluated with an Apgar score of 10 points. Laboratory investigations after birth revealed slightly

elevated infection markers, positive TOXO IgM and IgG antibody titers, and elevated bilirubin levels from the first day of life, which required phototherapy. Empirical antibiotic therapy was initiated, and blood and cerebrospinal fluid cultures identified Enterococcus spp. VRE+. The neonate was transferred to the Neonatal Pathology Department in stable condition with observable coarse tremors in the limbs and chin. He was placed in an incubator, continued on antibiotic therapy, phototherapy, and phenobarbital (Luminal) due to the observed seizure episodes.

After confirming positive IgM (1.520 S/CO) and IgG (524.60 IU/ml) TOXO antibody titers, as well as obtaining a blood sample for TOXO PCR testing, on the fourth day of life treatment for toxoplasmosis with sulfadiazine, pyrimethamine and folinic acid was initiated. Ultrasonography (USG) confirmed significant dilation of the brain ventricular system with asymmetry (L>P), rounded frontal horns of the lateral ventricles, and an Evans Index of 0.38. A computed tomography (CT) scan revealed massive irregular periventricular calcifications, with the ventricular system mainly expanded in the regions of the corpus callosum, occipital, and temporal horns of the lateral ventricles. Cerebrospinal fluid (CSF) was drained three times through lumbar punctures, with volumes of 35 mL, 30 mL, and 20 mL, respectively, on consecutive days and samples sent for general, bacteriological, and TOXO PCR analysis. The cerebrospinal fluid displayed significantly elevated protein levels (837.40 mg/dl), leading to the implantation of a Rickham reservoir. After implantation, the neonate remained stable, and protein levels gradually decreased (672.50 mg/dl on the second day post-implantation, 479.10 mg/dl on the sixth day, and 257.80 mg/dl on the fifteenth day). Due to reduced urine output on the sixth day and episodes of apnea, along with an elevated creatinine level (up to 1.00 mg/dl), treatment for toxoplasmosis was temporarily discontinued. Following the normalization of the test results, the reinitiation of medication was delayed due to the unavailability of folinic acid. The neonate underwent multiple ophthalmological evaluations, which did not reveal deviations from the norm. Serial transfontanelle USGs showed no changes compared to previous examinations, and abdominal ultrasounds did not detect any abnormalities.

At the 19th day post-implantation, with protein levels at 300 mg %, the neonate underwent the placement of a ventriculoperitoneal shunt. Due to an increase in cerebrospinal fluid leukocyte count (25 cells/µl on the sixth

postoperative day and 195 cells/µl on the tenth day) and protein levels in the drained fluid (407.50 mg/dl on the sixth day and 912.10 mg/dl on the tenth day), the decision was made to remove the ventriculoperitoneal drainage system and establish external drainage. After 21 days, anti toxoplasmosis treatment was resumed.

At three months of age, the neonate was readmitted to the Infant Pathology Department due to episodic seizures, including head turning to the right, upward eye deviation, extension of upper limbs, and flexion of lower limbs. Diagnostic imaging, including transfontanelle ultrasound and computed tomography, showed no changes compared to previous examinations. A consultation with neurology led to the prescription of diazepam (Relsed) 5mg/2.5 ml for rectal administration in the event of seizures lasting longer than five minutes. Following an EEG assessment during sleep and neurologic consultation around the fourth month of life, antiepileptic treatment was initiated, starting with phenobarbital (Luminal) and later adding valproic acid (Convulex) and Levetiracetam. At 12 months of age, the patient was admitted to the Department of Neonatal Pathology due to respiratory distress with numerous abnormal findings on auscultation. Rhinovirus/Enterovirus co-infection was confirmed. Respiratory secretion cultures grew Candida albicans, Enterobacter cloacae, and Stenotrophomonas maltophilia. Serological testing for Pneumocystis carinii (jiroveci) showed a positive IgG titer with negative IgM. Treatment included antibiotic therapy with Biseptol (sulfamethoxazole + trimethoprim), inhaled medications, such as Ambroxol and saline, as well as systemic steroid therapy. Throughout the hospitalization, the patient underwent multiple consultations with pulmonologists and laryngologists, with no identifiable causes for the hoarse breathing noted. Cardiological assessments were also performed due to recurrent rhythm disturbances recorded in the 24-hour Holter monitor. After overall condition stabilized, the patient was discharged to home hospice care with recommendations for continuing the ongoing treatments for toxoplasmosis, epilepsy, and ambulatory management of the infection.

DISCUSSION

In the neonatal period, only 10-20% of children display clinical symptoms of congenital toxoplasmosis, and none of these symptoms are pathognomonic. The characteristic Sabina-Pinkerton triad consisting of chorioretinitis, hydrocephalus, and intracranial calcifications cannot be employed as an exclusive diagnostic criterion for congenital toxoplasmosis, as it would result in the underdiagnosis of a significant number of cases. [20] More commonly, non-specific signs of congenital generalized infection may manifest, such as intrauterine growth restriction, severe and prolonged jaundice, hepatosplenomegaly, skin petechiae, muscle tone disturbances, reveal elevated inflammatory markers, increased aminotransferase activity or pleocytosis in cerebrospinal fluid. However, in 70-90% of cases of congenital toxoplasmosis, the initial course remains asymptomatic or subclinical, with these mentioned symptoms appearing later on. [6;7;9;14] The infection in the presented patient occurred during the critical period of organogenesis, between 10 and 24 weeks of gestation. However, treatment for the mother was initiated as late as the 16th week of gestation. Consequently, the child exhibited typical congenital toxoplasmosis symptoms, with a predominant presentation of hydrocephalus, after birth. Additionally, irrespective of the initial disease course, untreated congenital toxoplasmosis can lead to long-term complications that manifest during adolescence. Complications most often involve the visual system, potentially resulting in blindness, as well as central nervous system disorders, including seizures and intellectual developmental impairment. [7]

Because infection is usually asymptomatic and a vaccine is not available, education and prenatal screening tests are crucial. [2;8] Serologic tests to detect immunoglobulins specific to Toxoplasma (IgG and IgM) should be offered during preconception care and at the first prenatal visit, ideally early in the first trimester of pregnancy. [1;5] The differentiation of acute and chronic infections can be done using IgG avidity tests. High IgG avidity indicates chronic infection (more than four months), which significantly reduces the risk to the fetus. [1;9]

The optimal approach involves conducting assessments on women before a planned pregnancy. In Poland, the mandatory screening includes IgG and IgM Toxoplasma antibodies, which should be performed during the first gynecological examination in pregnancy, ideally between the 7th and 8th weeks of gestation. In

the case of a negative serological test result, it is necessary to continue serological testing throughout the pregnancy (at the beginning of pregnancy, around 24 weeks of pregnancy, and 2 weeks before the due date of delivery). Fetal diagnostics include the examination of the amniotic fluid (amniocentesis after 18-21 weeks of pregnancy). [13;16;19] In contrast, the United States, Canada, the United Kingdom, and some parts of Europe discourage routine universal screening for toxoplasmosis during pregnancy due to the low frequency of disease occurrence and maternal infection rates. [1]

Two possible protocols for the prophylaxis of congenital toxoplasmosis in women with a positive test result during pregnancy exist. Spiramycin is typically used to prevent fetal infection. Another option is a combination of pyrimethamine and sulfonamides (PS), but this should be avoided before the 14th week of pregnancy. In cases of pyrimethamine-sulfonamide treatment, folinic acid supplementation is required. [5] Research suggests that maternal treatment with spiramycin early in pregnancy reduces the transmission rate to the fetus from 56% to 24%. However, if maternal seroconversion has already occurred during pregnancy, treatment may not decrease the risk of transmission but can minimize severe congenital infection. [9] One of the few randomized clinical trials suggested that the P-S (pyrimethamine-sulfadiazine) protocol was more effective than spiramycin in preventing congenital toxoplasmosis (CT) in cases where the mother had seroconverted to toxoplasmosis during pregnancy. Moreover, the frequency of prenatal ultrasound brain abnormalities was significantly lower in the group receiving P-S compared to spiramycin (S). However, due to the small sample size, these results did not achieve statistical significance. [10;12] Previous randomized observational studies also provide indications that the transmission rate is lower when using the P-S protocol or the Austrian protocol (P-S for four weeks alternating with spiramycin) after the 16th week of pregnancy compared to using spiramycin alone. [2;12;14]

The most commonly employed treatment regimen for confirmed and probable cases of CT combines pyrimethamine, sulfonamide (sulfadiazine or sulfadoxine), and folinic acid for 12 months. The treatment protocols include pyrimethamine + sulfadiazine + folinic acid, pyrimethamine + sulfadoxine + folinic acid, or a mixed regimen where pyrimethamine and sulfadiazine are used for the first two months and sulfadoxine-pyrimethamine for the remaining ten months. [5]

In cases of severe disease with more than three intracranial calcifications and more than one ocular symptom or severe postnatal abnormalities, extended treatment (2 years) might be necessary. Long-term treatment may lead to adverse effects such as bone marrow suppression causing neutropenia, renal impairment, and allergic reactions. Close monitoring of blood morphology and periodic liver and kidney function tests are essential. [3] Therefore, in presented case, a temporary interruption of antiparasitic therapy was decided upon when renal parameters deteriorated. Unfortunately, a clinically significant delay in reinitiating the treatment occurred due to the unavailability of folinic acid. Typically, adverse effects are more severe when combining sulfadoxine and pyrimethamine than with pyrimethamine-sulfadiazine, with most common occurrences observed within the first two months of treatment. [5;10] During treatment, breastfeeding is not contraindicated, and vaccination programs should be conducted in accordance with local guidelines. Continuous clinical and ophthalmologic monitoring is imperative during and after treatment. [5]

CONCLUSION

Screening tests are important to enable early intervention and prevent long-term complications. [17;18] These screenings provide: primary prevention, which involves adhering to hygiene and precautionary measures and conducting subsequent screenings in the later stages of pregnancy; prophylactic therapy to reduce the risk of placental transmission in cases of primary maternal infection during pregnancy; and prenatal diagnosis through amniocentesis and rapid therapy to minimize complications in cases of congenital toxoplasmosis. [2;18] Routine counseling for pregnant women is essential to raise awareness about the infection, allowing them to take necessary preventive measures. This includes hygiene practices, avoiding the consumption of contaminated water or undercooked meat, and steering clear of contact with cat litter and soil in environments where cats may excrete T. gondii oocysts in their feces. [6;9]

Further research into the effectiveness of various treatment protocols, the risk of adverse effects, and the efficacy of new drugs is necessary. Studies comparing the use of P-S or Spy with alternative options such as cotrimoxazole, azithromycin, clindamycin, or atovaquone in combination with pyrimethamine or

other drugs are warranted. [3;12] However, the absence of randomized controlled trials and the significant heterogeneity in published retrospective cohort studies currently impede statistically significant analysis. [2;13]

Author's contribution

Conceptualization: Emilia Kowalczyk and Sylwia Koziej; methodology: Emilia Kowalczyk, Sylwia Koziej, Martyna Niemczuk and Adrianna Jasiuk; software: Emilia Kowalczyk, Mateusz Wiekiera; check: Sylwia Koziej, Mateusz Wiekiera and Adrianna Jasiuk; formal analysis: Emilia Kowalczyk, Sylwia Koziej, Martyna Niemczuk, Adrianna Jasiuk, Mateusz Wiekiera; investigation: Emilia Kowalczyk, Martyna Niemczuk, Mateusz Wiekiera; resources: Sylwia Koziej, Martyna Niemczuk; data curation: Adrianna Jasiuk, Mateusz Wiekiera; writing - rough preparation: Emilia Kowalczyk, Sylwia Koziej, Martyna Niemczuk, Adrianna Jasiuk, Mateusz Wiekiera; writing - review and editing: Emilia Kowalczyk, Sylwia Koziej; visualization: Emilia Kowalczyk; supervision: Emilia Kowalczyk; project administration: Emilia Kowalczyk, Adrianna Jasiuk.

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