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Congenital Toxoplasmosis and Long-term Outcomes

Konjenital Toksoplazmozis ve Uzun Dönem Sonuçları

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ABSTRACT

Objective: Congenital toxoplasmosis (CT) can have severe early and late sequelae in children. In this study, we aimed to evaluate the demographic, clinical, treatment characteristics of patients diagnosed with congenital *Toxoplasma* infection and to highlight the long-term complications of the patients.

Methods: Patients with CT were included in this study who were followed between 2010 and 2022 in Cukurova University Medical Faculty Hospital. Demographic, clinical and treatment characteristics were searched retrospectively. In the diagnosis of maternal and CT, *Toxoplasma* IgM, IgG, IgG avidity, *T. gondii* polymerase chain reaction tests were used along with clinical and symptoms.

Results: Eighteen children (two twins) with CT and their mothers (n=16) were included in the study. Median age was 1 month. Ten (55.5%) of the children were male. CT diagnosis was made during pregnancy in 7 mothers (resulting in 8 babies) and postnatally in 9 mothers (resulting in 10 babies). The mothers of 5 (31.1%) babies with CT received spiramycin treatment during pregnancy. Three (60%) of 5 pregnant women who received spiramycin were diagnosed in the first trimester, 4 (80%) of the babies did not have any sequale and only 1 (20%) had microphthalmia. Ocular involvement was the most common presentation of the disease occured in 10 patients (55.5%), hydrocephalus and intracranial calcification developed in five patients (27.7%). Hearing loss developed in 2 (11.1%) patients. During the follow-up period, seizures developed in 3 patients (16.6%), microcephaly in 2 patients (11.1%), and neurodevolopmental retardation in 7 patients (38.8%), two of the patients had severe mental retardation. One (5.5%) patient with hydrocephalus died at 36 months of age due to complications after ventriculoperitoneal shunt application.

Conclusion: In our study, we observed severe sequelae in vision, hearing, and neurodevelopmental aspects in children diagnosed with CT at birth and during follow-ups. Early diagnosis and treatment of infants, along with the detection of *Toxoplasma* infection during pregnancy, are essential in preventing severe sequelae that may arise due to CT.

Keywords: Congenital toxoplasmosis, children, chorioretinitis

ÖZ

Amaç: Konjenital toksoplazma enfeksiyonu çocuklarda erken ve geç dönemde ağır sekellere neden olur. Biz bu çalışmada konjenital toksoplazma tanısı alan hastaların demografik, klinik, tanı, tedavi özelliklerini ve hastaların uzun dönemde gelişen komplikasyonlarını değerlendirmeyi amaçladık.

Yöntemler: Bu çalışmada Çukurova Üniversitesi Tıp Fakültesi Hastanesi'nde 2010-2022 yılları arasında konjenital *Toksoplazma* enfeksiyonu saptanan bebeklerin demografik, klinik, tanı, tedavi özellikleri ve prognozları retrospektif olarak değerlendirilmiştir. Maternal ve konjenital *Toxoplasma* enfeksiyonu tanısında, klinik belirti ve bulgularla birlikte *Toxoplasma* IgM, IgG ve IgG avidite, *T. gondii* polimeraz zincir reaksiyon testleri kullanıldı.

Bulgular: Bu çalışmaya medyan yaşı 1 ay olan 10'u (%55,5) erkek, ikisi ikiz olan 18 konjenital *Toxoplasma* tanısı alan bebek ve bu bebeklerin anneleri (n=16) dahil edildi. Konjenital *Toxoplasma* tanısı, 7 annede gebelik sırasında (bunların 8 bebeği) ve 9 annede doğum sonrasında (bunların 10 bebeği) konuldu. Konjenital toksoplazmalı bebeklerin 5'inin (%31,1) annesinin gebeliğinde

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spiramisin tedavisi aldığı belirlendi. Spiramisin alan 5 gebeden 3'ünün (%60) ilk trimestarda tanı almasına rağmen bebeklerin 4'ünde organ tutulumu olmayıp yalnızca 1'inde mikroftalmi mevcut idi. Konjenital *Toxoplasma* tanısı alan bebeklerin tanı anında en sık 10 (%55,5) hastada göz tutulumu olduğu ve hastaların 5'inde (%27,7) hidrosefali ve intrakraniyal kalsifikasyon olduğu saptandı. İki (%11,1) hastada işitme kaybı geliştiği belirlendi. İzlemde 3 hastada (%16,6) nöbet, 2 hastada (%11,1) mikrosefali ve ikisi ağır mental retardasyon olan 7 hastada (%38,8) nörogelişimsel gerilik olduğu saptandı. Bir (%5,5) hastanın 36 aylıkken hidrosefali ve ventriküloperitoneal şant uygulanması sonrası gelişen komplikasyonlar nedeniyle yaşamını yitirdiği saptandı.
Sonuç: Çalışmamızda, doğumda ve takiplerde konjenital *Toxoplasma* tanısı konulan çocuklarda görme, işitme ve nörogelişimsel alanlarda ciddi sonuçlar gözlemledik. Bebeklerin erken tanı ve tedavisi ile birlikte gebelikte *Toxoplasma* enfeksiyonunun tespiti, konjenital *Toxoplasma* kaynaklı ciddi sonuçların önlenmesinde esastır.
Anahtar Kelimeler: Konjenital toksoplazmozis, çocuk, koryoretinit

INTRODUCTION

Toxoplasma gondii (*T. gondii*) is one of the most common zoonotic agents seen in humans, and its incidence varies according to geography and socio-economic characteristics. It is especially common in Europe, Central America, Brazil and Central Africa (1). In a recent study in our country, anti-*T. gondii* IgG and IgM antibodies have been reported between 17.5-69.5%, and between 0-5.4% respectively (2).

In a study evaluating 817 pregnant women in our country, the seroprevalence of *Toxoplasma* was determined to be 36.2%. Among pregnant women from the Southeastern Anatolia region, 47.1% exhibited *Toxoplasma* IgG positivity, whereas in those from the West region, this rate was found to be 30.1% (3). In our country, data regarding the frequency of congenital toxoplasmosis (CT) in children, aside from case presentations, are limited.

Felidae family members; is the only definitive host of *T. gondii*. There are 3 forms of the parasite during infection. These; are called tachyzoite (stage where they are found in groups or individually), bradyzoite (stage where they are found in tissue cysts) and sporozoite (stage where they are found in oocysts outside the host). Ingestion of oocysts excreted in feces of cats and consumption of raw or undercooked meat containing bradyzoite forms are considered to be the most important transmission routes for *Toxoplasma* infection (4).

CT occurs as a result of *T. gondii* crossing the placenta and infecting the baby. Majority of the infection is due to primary infections during pregnancy. Infection during pregnancy can cause severe complications that can lead to fetal death. Even if the baby has no signs at birth, it may cause learning disabilities, seizures, hydrocephalus, hearing disorders, chorioretinitis, retinal scarring, and visual disturbances in the late period.

Vertical transmission varies depending on the gestational age, the trimester in which the pregnant woman had primary infection, and the antenatal treatment. While the rate of transmission to the baby in untreated pregnant women is 10-15% in the first trimester, it has been reported to be 70-80% in the third trimester (4-6).

The diagnosis of CT relies on the history and serology of the mother's exposure to *Toxoplasma* during pregnancy, the baby's *Toxoplasma* serology, and clinical features. *Toxoplasma* IgM may be negative in 20-50% of CT cases. Positive *Toxoplasma* IgG alone is not conclusive, as it may indicate maternal antibody transfer; thus, its value should be compared with the mother's IgG levels and evaluated based on follow-up values. Assessing avidity values of anti-*T. gondii* antibodies, along with IgG and IgM antibodies, in the first trimester of pregnancy can aid in distinguishing between past and recent infections (4,7,8). It has been reported that effective treatment during pregnancy reduces the rate of severe neurological sequelae by 75% in infants who develop CT (9). Early diagnosis and initiation of effective treatment of CT play an important role in indicating the prognosis (7).

It was aimed to evaluate the demographic, clinical, diagnostic and treatment characteristics and long-term complications of patients diagnosed with CT.

METHODS

Study Population

Eighteen babies diagnosed with CT in Cukurova University Medical Faculty Hospital between 2010-2022 and their mothers (n=16) were included in the study. On February 4, 2023, at the 130th meeting of the Çukurova University Faculty of Medicine Ethics Committee, ethical approval was obtained for this study.

Maternal Infection and Prenatal Diagnosis of CT

Diagnosis of maternal infection was based on detection of *Toxoplasma* IgM and IgG (toxo IgM, toxo IgG) antibodies Acqusition of the *Toxoplasma* infection was based on seroconversion during pregnancy or on determination of IgG avidity and kinetics of antibodies (8). Toxo IgG, toxo IgM was studied by electrochemiluminescence method in Cobas e-601 Roche (Netherlands) device and microparticular enzyme immunoassay method in Abbott Architec I 2000 (USA) device. Toxo IgG avidity test was studied by micro ELISA method (Diapro marks kit, Milan/Italy).

Postnatal Diagnosis of CT

Congenital infection was diagnosed by any of the following: 1) Increase in Toxo IgG titer during the first year of life or increasing toxo IgG titer compared with the mother's; 2) Positive toxo IgG with positive toxo IgM; 3) Positive *T. gondii* polymerase chain reaction (PCR) test in cerebrospinal fluid (CSF), blood or urine; 4) Positive Toxo IgG beyond 12 months of age, and 5) Infants with characteristic clinical findings, positive toxo IgG, but negative toxo IgM (8).

Clinical and laboratory characteristics at birth and the results of eye examination and hearing test performed by specialist doctors were searched from the files of pediatric patients during the clinical follow-up, ocular findings, hearing findings, neurological complications and neurodevelopmental evaluation results were recorded.

Statistical Analysis

Statistical analyses were completed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Data are presented as medians (minimum-maximum) and as n (%). Correlation analysis was used to search the realation between treatment prophylaxis and outcomes.

RESULTS

Toxoplasma IgM positivity was detected in 314 pregnant women in Cukurova University Hospital between 2010 and 2022. Eighteen infants, two of whom were twins, diagnosed with CT and their mothers (n=16) were included in the study. There were a total of 18 children born to 16 mothers who had experienced *Toxoplasma* infection. CT diagnosis was made during pregnancy in 7 mothers (resulting in 8 babies) and postnatally in 9 mothers (resulting in 10 babies). Demographic and clinical characteristics of mothers of infants with congenital *Toxoplasma* are demonstrated in Table 1.

The mothers of five of the babies diagnosed with CT used spiramycin during pregnancy, and three of these babies were diagnosed in the first trimester. Microphthalmia was detected in only one of five patients whose mothers used spiramycin during pregnancy, and there were no organ involvement in the other babies.

Ten (55.5%) of the infants with CT were male and eight (44.5%) were female. The median age at admission was one month. Fourteen of the patients (77.7%) were diagnosed in the first month, while the other four patients were diagnosed at 2, 5, 6, and 9 months of age. Demographic data of infants with CT are demonstrated in Table 2.

Clinical findings consistent with CT at birth was reported in 11 (61.1%) babies. Three patients presented with growth retardation and inability to gain weight, one patient had a deviation in the eyes, one patient had opacities in the eyes and one patient had muscle weakness. Ocular findings were reported in 10 (55.5%) of the patients. Chorioretinitis was present in eight patients (44.4%) in total, and active chorioretinitis was found in six of these patients. Retinal scar, which was thought due to chorioretinitis, was detected in seven patients, and five of these patients had macular involvement. The clinical findings of the patients at the time of diagnosis are demonstrated in Table 3.

Initial laboratory parameters and cranial imaging results of infants diagnosed with CT are demonstrated in Table 4. Although 8 (44.4%) patients had toxo IgM at the time of diagnosis, all patients (100%) had *Toxoplasma* IgG antibody. Nine of the toxoplasmosis-infected infants (50%) had mothers with available *Toxoplasma* avidity results, with 4% of these patients (44.4%) exhibiting high *Toxoplasma* avidity and 5% (55.5%) having low avidity. Evaluation of avidity results indicated that all these mothers likely experienced *Toxoplasma* infection during pregnancy. Among the eight infants who underwent lumbar puncture, *Toxoplasma* PCR was examined in four cases (50%), and it was determined to be negative in the CSF.

It was determined that 16 of the patients were evaluated by cranial ultrasound (USG), 14 of them by cranial tomography and 7 of them by cranial magnetic resonance imaging (MRI). Hydrocephalus was reported in 6 patients by cranial USG,

Table 1. Demographic and clinical characteristics of mothers of infants with congenital toxoplasmosis

	n=16	%
Age, median (min-max)	25 (19-37)	
Raw meat consumption, n (%)	5	31.2
Animal exposures, n (%)	5	31.2
Gravida median (min-max)	1 (1-4)	
Abnormal fetal USG, n (%)	5	31.2
Toxo IgM positivity in pregnancy, n (%)	7	43.7
Flu-like symptom, n (%)	3	18.7
Time of diagnosis of *Toxoplasma* infection, n (%) First trimester Second trimester Third trimester Postnatal	 3 0 4 9	 18.7 0 25 56.2
Spiramycin treatment, n (%)	5	31.2

USG: Ultrasound

Table 2. Demographic data of infants with congenital toxoplasmosis

Data	
Actual age (month), median (min-max)	79 (5-153)
Age at diagnosis (month), median (min-max)	1 (1-9)
Gender n (%) Female Male	 8 (44.5) 10 (55.5)
Prematurity rate, n, (%) **Gestational age of premature babies,** median (min-max)	7 (38.8%) 34 (32-37)
Small gestational age n, (%)	1 (5.5%)
Hospital admission at birth, n, (%)	9 (50%)
The median follow-up period (years), median (min-max)	6.3 (3 month-12.6 year)

Table 3. Clinical findings of infants with congenital toxoplasmosis at the time of diagnosis

Data	n=18	%
Ocular involvement, n, (%) Chorioretinitis, Active chorioretinitis, Retinal scar Microophthalmia Cataract	10 8 6 7 6 2	55.5 44.4 33.3 38.8 33.3 11.1
Abnormal universal newborn screening, testing Hearing loss [confirmed with auditory brainstem response (ABR)]	4 1	22.2 5.5
Macrocephaly	2	11.1
Microcephaly	1	5.5
Hydrocephaly	5	27.7
Seizure	2	11.1
Icterus	5	27.7
Cholestasis	1	5.5
Hepatomegaly	4	22.2
Splenomegaly	3	16.6
Hepatosplenomegali	3	16.6
Ascites	2	11.1
Rash	2	11.1

Table 4. Laboratory and cranial imaging findings in babies with congenital toxoplasmosis at the time of diagnosis

Data	
White blood cell/µL median, (min-max)	9775 (3000-15570)
Number of patients with high ALT	2 (11.1%)
Number of patients with high biluribin	3 (16.6%)
Number of patients with cholestasis	2 (11.1%)
Number of patients with *Toxoplasma* IgM positivity, n, (%) Toxo IgM value, median, (min-max)	8 (44.4) 0.39 (0.19-27.6)
Number of patients with *Toxoplasma* IgG positivity n, (%) Toxo IgG value, median, (min-max)	18 (100) 650 (200-656)
Cranial USG, n=16, (%) Normal Ventriculomegaly-hydrocephaly Intracranial calcification Increased echogenicity in basal ganglia	 7 (38.8) 6 (33.3%) 3 (16.6%) 2 (11.1%)
Cranial tomography, n=14, (%) Normal Intracranial calcification Serebral atrophy Hydrocephaly	 9 (50) 5 (27.7%) 2 (11.1%) 5 (27.7%)
Cranial MRI, n=7, (%) Normal Intracranial calcification Hydrocephaly	 5 (27.7) 2 (11.1) 2 (11.1)

MRI: Magnetic resonance imaging, ALT: Alanine transaminase, USG: Ultrasound

however there were 4 patients with hydrocephalus confirmed with cranial tomography 1 patient in cranial MRI during the follow-up. Intracranial calcification was present in 5 patients (27.7%) on cranial tomography.

Primetamine, sulfadiazine and folinic acid treatment was started in all diagnosed patients. Bactrim and clindamycin treatment was started in 2 patients until the drug was obtained. All patients were treated for 12 months, and 1 patient, who was 5 months old, was still under treatment. Steroid treatment was given patients with active chorioretinitis. In the follow-up period, one (5.5%) patient died at 36 months of age due to hydrocephalus and complications developed after ventriculoperitoneal shunt application.

The median follow-up period of babies diagnosed with congenital *Toxoplasma* was 6.3 years (minimum: 3 months-maximum: 12.6 years). In the follow-up, nystagmus developed in a patient with a history of previous ocular findings. Hearing tests of 4 patients were abnormal in the neonatal period, however confirmed hearing loss was diagnosed in 1 patient upon further examination. The second patient diagnosed with hearing loss complained of speech delay who had a normal newborn hearing screening test however developed hearing loss in the follow-up period. Hearing loss developed a total of two (11.1%) patients. During the follow-up, three (16.6%) patients developed seizures. Microcephaly occured in two (11.1%) patients, and neurodevelopmental retardation was observed in seven (38.8%) patients, including severe mental retardation in two patients.

DISCUSSION

Although a decrease in seropositivity for *T. gondii* has been reported in the past decades, it is estimated that one third of the world's population is infected with *T. gondii*. In a retrospective study evaluating 1,037 pregnant women in 2022, *Toxoplasma* seroprevalence was reported as 52.6%, seroconversion rate as 3.4% and congenital infection rate as 0.2% (10).

In our study, it was determined that 314 pregnant women had toxo IgM positivity in a 12-year period and 18 babies were diagnosed with CT during this period. We consider that the number of babies with CT is higher because all of the pregnant women who were found to have seroconversion for *Toxoplasma* could not be followed up in our hospital and asymptomatic babies might not have been diagnosed during the follow-up.

Contact of pregnant women with oocysts excreted with feces of cats, ingestion of oocysts through food, and consumption of raw or undercooked meat and ingestion of bradyzoite forms are the most important ways of transmission of congenital *Toxoplasma*. Recipients can become infected by transfusion of blood and organs from donors infected with *T. gondii* (4,8). The high consumption of traditional food made with raw meat in our region increases the mother's exposure to toxoplasmosis. In our study, 31.2% of mothers of infants with congenital *Toxoplasma* had a history of eating uncooked or raw meat. In addition, 31.2% of the mothers had cat and animal contact.

Acute maternal infection is often (>50%) asymptomatic. Generally, there are flu-like findings such as mild fever, sweating, headache, myalgia, pharyngitis, which last 2-3 days in pregnant women. Hepatosplenomegaly, lymphadenopathy, and maculopapular rash may be present (4). In our study, 3 (18.75%) of the mothers had a flu-like finding in their pregnancy.

Although there are conflicting results that the use of spiramycin during pregnancy prevents the development of CT, today the recommendation to use spiramycin remains valid in the first 14 weeks when toxoplasma infection is detected in pregnant women. If there is a high risk for congenital *Toxoplasma* infection

after the 14th week, it is generally recommended to switch to the combination of pyrimethamine-sulfadiazine and folinic acid and to decide on the treatment according to the amniocentesis result at the 18th week (7,11).

In a European observational study of a cohort of 293 infected fetuses of whom two-thirds received prenatal treatment, prenatal treatment was estimated to reduce the risk of serious neurologic sequelae or death by three-quarters (odds ratio: 0.24, 95% confidence interval: 0.07-0.71). After maternal seroconversion at 10 weeks of gestation, the estimated absolute risk of serious neurologic sequelae or death in treated and untreated pregnancies was 25.7 and 60.0 percent, respectively (9). In congenital *Toxoplasma* infection, the development of infection in the first trimester causes severe sequelae and even intrauterine death, while the risk of transmission of *Toxoplasma* to the baby increases in the advancing gestational week, the risk of developing severe infection decreases. Detection of congenital infection in the early period and initiation of antiparasitic treatment during pregnancy, can prevent the severe complications that may develop (8,9).

Among our patients with CT spiramycin treatment was initiated in 31.5% (5 of 16) of the mothers. In our study, when the babies of pregnant women who received spiramycin were evaluated although three of five pregnant women were infected in the first trimester, only one baby had microphthalmia and the other babies did not have any organ involvement.

Intrauterine *Toxoplasma* infection has been associated with decreased gestational age. In the study of Freeman et al. (12), the prematurity rate in the babies of mothers with *Toxoplasma* infection during pregnancy was 25%, while this rate was 9% in babies of uninfected mothers. In our study, prematurity rate was 38.8%.

Approximately 10-30% of infants with congenital infection have clinical signs and symptoms at birth and in early infancy. Clinical findings vary according to the organ involved in the congenital infection. Chorioretinitis, intracranial calcification, and hydrocephalus, also known as the classical triad, is the most common finding in the diagnosis of CT (4,13).

In our study, 11 (61.1%) patients had clinical signs and symptoms at the time of diagnosis. Since our study is not a prospective study including the follow-up of pregnant women, we consider that asymptomatic and mild cases have not been fully determined. Similar to the literature, the most common presentation in patients diagnosed with CT was (55.5%) eye involvement, and 44.4% of the eye involvement was chorioretinitis, In addition hydrocephalus. Hepatomegaly, intracranial calcification was found in 27.7%, 22.2% and. 27.7% of the patients respectively.

The eye is the most frequently involved organ in children with CT. In the 15-year follow-up of children with CT diagnosed in a national reference laboratory in the USA, chorioretinitis was reported in 92% of the infants. Chorioretinitis was the most common complication in the late period. The rate of development of new lesions in untreated children was reported in 90% of the patients (8,14).

In a study conducted in Brazil, 71.4% of the cases had chorioretinitis in early infancy, and the probability of developing new lesions in patients treated in the first two months of life, and the severity of the disease was lower than those treated after 4 months of life (15).

In our study, eye involvement was found in 55.5% of our patients in the early infancy period and chorioretinitis was found in 44.4%. Active lesion was present in 6 of the patients with chorioretinitis. Retinal scar was present in 7 of the patients with chorioretinitis, and 5 of these patients had scars in the macula. In this study, the median age of the patients was one month and the treatment was started within the first two months, of age in 15 babies. Among the patients with CT complicated with chorioretinitis no new lesions were observed during the follow-up.

In addition to chorioretinitis, patients may have involvement such as microphthalmia, macular atrophy, macular scar, cataract, and strabismus. Macular involvement has been reported in 54% of children with CT in North America (16). In our study, microphthalmia was occured in 6 (33.3%) patients, macular atrophy and scarring in 5 (27%), and cataract in 2 (11.1%) patients. In the follow-up of period nystagmus developed in 1 (5.5%) patient. In view of the fact that chorioretinitis can develop up to time of adolescence, eye examination and follow-up were performed at regular intervals.

Congenital *Toxoplasma* is a known cause of hearing loss in infants. However, data related to its frequency and type of hearing loss are limited in the literature. It is recommended to perform the more sensitive auditory brainstem response (ABR) test instead of routine hearing tests in symptomatic newborns. Early diagnosis and appropriate treatment reduce its poor prognosis and rarely develop hearing loss (17). In a study which evaluated 24 children with CT hearing loss was identified in patients between 22 and 30% (18).

In a study in which 30 infants with CT were evaluated in the first two months of their lives, sensorineural hearing loss was not indentified in the patients, but conductive hearing loss associated with otitis media was identified in 20% of the patients (19). In the evaluation of 106 infants with CT central hearing impairment was identified in 27.4% of the infants, conductive and sensorineural hearing loss was identified in 12.3% and 3.8% of the patients respectively (20). In our study, a total of 2 (11.1%) patients were identified to have hearing loss one of the patient developed hearing loss after birth during follow-up period. The exact ratio of the number of patients with hearing loss is not known, as routine ABR testing was not performed on the patients in our study.

The incidence of hydrocephalus has been reported between 30 and 68% in infants with CT.

In a study conducted in 120 infants with CT, 96 of whom had severe clinical findings it was reported that intracranial calcification with hydrocephalus was detected at a rate of 50% hydrocephalus can develops more likely in untreated patients with CT (21). In our study, hydrocephalus occured in 5 (27.7%) patients, ventriculoperitoneal shunt was placed in three patients and one patient died due to ventriculoperitoneal shunt complication.

In our study, microcephaly observed in 1 patient at the time of diagnosis, and microcephaly developed in 2 more patients during the follow-up, and microcephaly was detected in total of 3 (16.6%) patients. In the literature, the incidence of microcephaly in infants with CT has been reported to be 15% (8).

It has been reported that 20% of children with CT may develop seizures, 30-35% hepatosplenomegaly, 25% rash and 60% jaundice (21). In our study, seizures reported in total of 5 (27.7%) patients, 2 (11.1%) patients at the diagnosis and 3 patients developed during follow-up period, 4 patients (22.2%) developed hepatomegaly and 3 patients (16.6%) hepatosplenomegaly, 2

(11.1%) patients developed rash in the neonatal period and 5 (27.7%) patients developed jaundice. Cholestasis was determined in 2 (11.1%) patients who jaundice.

The diagnosis of CT is based on the mother's history and serology of toxoplasmosis during pregnancy, the infant's *Toxoplasma* serology and clinical features. Toxo IgM antibodies can be detected about 1 week after infection and remain elevated for several months or years. Congenital and acquired acute *Toxoplasma* infections can be diagnosed with the detection of. IgM antibodies of *T. gondii*. Negative IgM antibody may be present in 20-50% of patients with CT. Negative IgM antibody was reported more frequently in patients whose mothers received treatment before delivery. *Toxoplasma* IgG antibodies are usually detected 1-2 weeks after infection, reach their highest value within 1-2 months, and usually remain at a certain level for life (8). In newborns CT is mostly asymptomatic. It is hard to make a diagnosis without information on maternal serologic profile. Positive IgG and negative IgM antibodies in the first and second trimesters represents that the infection was acquired before the current pregnancy. If the initial testing is done in the third trimester, a negative IgM result will not rule out an infection acquired early in pregnancy (8). For the proper diagnosis of CT it is essential to determine paired control of antibodies both maternal and neonatal sera. IgG antibodies in infants up to one year or their increase in the first months, lead to diagnosis of CT. In our study, 8 (44.4%) of the babies had positive *Toxoplasma* IgM antibody at the time of initial diagnosis, and 18 (100) patients had positive IgG antibody.

In the diagnosis of CT, the evaluation of the avidity values of anti-*T. gondii* antibodies in conjunction with IgG and IgM antibodies in the first trimester of pregnancy can assist in distinguishing between past and recent infections. Depending on the method used, an individual with a high avidity value is presumed to have acquired the infection at least 3-5 months ago, while a low avidity value is considered indicative of a recent infection (4,7,8). In our study, the *Toxoplasma* avidity results were available for mothers of 9 (50%) CT infants, with 4% (44.4%) showing high avidity and 5% (55.5%) showing low avidity. Due to the examination of mothers at different trimesters and even postpartum in our study, the role of avidity in diagnosis was limited. However, avidity results indicate that all these mothers likely experienced *Toxoplasma* infection during pregnancy.

Lumbar puncture and cranial imaging are recommended in patients with clinically suspected CT. In the CSF examination, increase in bos protein, lymphocytes and monocytes count may be present in severe cases, CSF protein may be >1 gram. Positive *Toxoplasma* PCR can be detected (4). In our study, lumbar puncture was performed in 8 patients. Median CSF protein was 309 mg/dL. *Toxoplasma* PCR was negative in 4 patients.

While hydrocephalus and ventriculomegaly can be evaluated with cranial USG, calcification, focal brain lesions can be evaluated more sensitively with cranial tomography cranial MRI is also a sensitive imagine method in the diagnosis of CT however as a disadvantage it requires anesthesia. Intracranial calcification was reported in 50-85%, hydrocephalus in 30-68% of the patients with CT (8,21). In our study, hydrocephalus was determined in 5 (27.7%) of our patients and intracranial calcification was found in other 5 (27.7%) of our patients.

It is recommended to use a combination of pyrimethamine, sulfadiazine and folinic acid for 12 months in the treatment of CT. It has been reported that severe sequelae that may develop with early treatment can be prevented (16). The prognosis is generally poor in infants with obvious signs at birth. In the follow-up of 156 untreated infants with CT, 152 of whom had obvious signs, the reported mortality rate was 12%, mental retardation was 93%, seizure development was 81%, severe visual impairment (60%), hydrocephalus or microcephaly (33%), and deafness was 15%. In children with subclinical infection, sequelae may develop in the follow-up. However, there is insufficient data on the frequency and severity of these sequelae (23).

In our study, all patients diagnosed with congenital *Toxoplasma* received treatment consisting of pyrimethamine, sulfadiazine, and folinic acid. Two patients were treated with bactrim and clindamycin until the drug was obtained. In our study, the mortality rate of the patients in 12 years was 5.5%, the incidence of chorioretinitis-retinal scar was 44%, mental retardation was 38.8%, seizures was 27.7%, the rate of microcephaly development was 16.6%, and the rate of hearing loss was 11.1%.

CONCLUSION

Our investigation highlighted that the majority of congenital *Toxoplasma* cases were diagnosed post-pregnancy and during the third trimester. Beyond the initial severe impacts, infants with CT exhibited subsequent complications, including vision and hearing disorders, along with enduring severe mental effects during follow-ups. To effectively prevent congenital *Toxoplasma* infection, it is crucial to prioritize early diagnosis and treatment for infants, detect *Toxoplasma* infection during pregnancy, and ensure timely and appropriate treatment for pregnant women.

* Ethics

Ethics Committee Approval: On February 4, 2023, at the 130th meeting of the Cukurova University Faculty of Medicine Ethics Committee, ethical approval was obtained for this study.

Informed Consent: Retrospective study.

* Authorship Contributions

Concept: O.O.G., Z.H., E.E., D.A., U.C., F.O., F.K., S.C., Design: O.O.G., Z.H., E.E., D.A., U.C., F.O., F.K., S.C., Data Collection or Processing: O.O.G., Z.H., E.E., D.A., U.C., F.O., F.K., S.C., Analysis or Interpretation: O.O.G., Z.H., E.E., D.A., U.C., F.O., F.K., S.C., Literature Search: O.O.G., E.E., Writing: O.O.G., Z.H.

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