Ocular manifestation of congenital toxoplasmosis, clinical implication – case report

Manifestacja oczna wrodzonej toksoplazmozy, implikacje kliniczne – opis przypadku

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Abstract

The aim of this case report was to present extremely severe, ophthalmic complications in form of rare, congenital toxoplasmatic bilateral defect of eye-balls concomitant with advanced uveitis, microphthalmia and eye-multistructural developmental abnormalities leading to irreversible visual disability. The ocular diagnosis was confirmed in Ret-Cam II and ultrasonography and it was accompanied with congenital multiorgan lesions including hepato-splenomegaly, thrombocytopenia, leukomalacia, hydrocephalus and ventriculomegaly with neurological symptoms. Serology, PCR of cerebro-spinal fluid and cord blood confirmed the presence of congenital Toxoplasma gondii infection in the infant.

The authors took the effort of insightful analysis for the causes of applied treatment failure in mother during pregnancy, analyzing the inefficacy of Spiromycin therapy in pregnant woman and evaluating false-negative result of amniocentesis for Toxoplasma gondii presence.

Among many issues concerning anti-toxoplasmatic treatment in mother and infant presented in this article, the need for multiple repetition of toxoplasmatic tests should be underlined including amniotic fluid PCR and ultrasonography which can add much important data for correct diagnosis. The authors indicate that the lack of benefits from conservative therapy in case of suspected Toxopalsma gondii suggestion lead to dramatic multiorgan complications, especially ophthalmo-neurologic, leading to irreversible visual disability.

Key words: **congenital toxoplasmosis** / **diagnosis** / **treatment** / / **eye development – abnormality** / **multiorgan complications** /

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Otrzymano: **15.10.2014**
Zaakceptowano do druku: **21.02.2015**

Streszczenie

Cel pracy: *Celem doniesienia było przedstawienie wyjątkowo ciężkich, okulistycznych powikłań w postaci rzadkiego, wrodzonego toksoplazmatycznego uszkodzenia obustronnego gałek ocznych współistniejącego z zaawansowanym zapaleniem błony naczyniowej, małooczem i wielostrukturalnymi wadami rozwojowymi oka prowadzącymi do nieodwracalnego uszkodzenia widzenia. Rozpoznanie zostało potwierdzone w badaniach Ret-Cam-II i ultrasonograficznych. Zmianom okulistycznym towarzyszyły wrodzone nieprawidłowości wielonarządowe, w tym powiększenie śledziony i wątroby, trombocytopenia, zanik tkanki mózgowej, wodogłowie i powiększenie komór mózgu, objawy neurologiczne. Badania serologiczne, PCR płynu mózgowo-rdzeniowego i krwi pępowinowej potwierdziły u dziecka obecność wrodzonej infekcji Toxoplasma gondii.*

Autorzy podjęli wysiłek wnikliwej analizy przyczyn niepowodzeń zastosowanego leczenia u matki w czasie ciąży omawiając prawdopodobny termin zakażenia matki i płodu, analizując nieskuteczność terapii spiromycyną u ciężarnej oraz oceniając fałszywie ujemny wynik PCR płynu owodniowego płodu w kierunku obecności Toxoplasma gondii.

Spośród wielu kwestii dotyczących terapii przeciw-toksoplazmatycznej u matki i dziecka przedstawionych w artykule, zwraca uwagę konieczność wielokrotnego powtarzania badań laboratoryjnych, serologicznych, w tym PCR płynu owodniowego oraz ultrasonograficznych, wnoszących wiele ważnych informacji do rozpoznania toksoplazmozy. Autorzy wskazują, że brak efektu terapii zapobiegawczej w przypadku sugestii Toxoplasma gondii może prowadzić do dramatycznych powikłań wielonarządowych, szczególnie neuro-okulistycznych, prowadząc do nieodwracalnego w skutkach uszkodzenia widzenia.

Słowa kluczowe: **toksoplazmoza wrodzona** / **diagnostyka** / **leczenie** / / **wady rozwojowe oka** / **nieprawidłowości wielonarządowe** /

Introduction

Primary toxoplasmosis in pregnant woman poses a risk of intrauterine infection. The fetus becomes infected by *Toxoplama gondii (T. gondii)* after primary maternal infection and thereafter by transmission of the parasite through the placenta to the fetus. Estimated frequency of congenital toxoplasmosis occurrence amounts from 1 to 10 per 10 000 live births in the United States and Europe [1, 2]. In Poland, approximately 400 new cases annually are confirmed which constitutes around 1.1/1000 or 1.9/1000 live births from immunocompetent and immunocompromised pregnant women [3]. Toxoplasmosis contagiousness in first trimester of pregnancy is related to the highest risk of severe neurosensory symptoms in newborn, miscarriage or fetus death, their risk decrease with increasing gestational age [4–7].

Among neuro-ocular symptoms retinochoroiditis (80%), intracranial calcifications (about 40%), hydrocephalus or microcephaly (up to 20%) known as classical triad are described. Other symptoms comprise of congenital eye malformations (microphthalmia, oranophthalmia, congenital cataract, blindness, strabismus), encephalitis, confusion, seizures, focal neurological deficits, cerebellar abnormalities, pneumonitis, with respiratory failure and amblyacousia. Second trimester manifestations are similar to bacterial sepsis ("acute" infection period) including hepatosplenomegaly and lymphadenopathy, encephalitis, pneumonitis and icterus. Infection during the last weeks of pregnancy usually has no apparent clinical manifestation in newborn at birth (85–90%) [4-6].

The aim of this case report was presentation of a newborn with extremely rare congenital bilateral eye-ball toxoplasmatic defect in the form of different eye-structures deterioration concomitant with retinochorioiditis leading to probable permanent, irreversible visual disability in the future. Simultaneously, the authors took the effort of analysis for the treatment failure causes in the pregnant woman and her baby.

Case description

Obstetric data showed that in 18th week of pregnancy the baby's mother was diagnosed with asymptomatic acute form of *T. gondii* infection. The serological tests performed at that time confirmed the presence of anti Toxo-antibodies IgM-5.0 COI and IgG-630 IU/ml with zero avidity (the referential values for IgG absence <1.0; equivocal 1.0 - 29.9; presence>30; IgM absence<0.8 equivocal 0.81-0.99, presence>1.0). Therefore, spiromycin prophylaxis (rovamycin – macrolide) was implemented.

The follow-up tests in 24 gestational age (GA) still disclosed gradually decreasing the anti-*T.gondii*: IgM-2.8 COI, IgG- 287 IU/ml with 0.19 avidity, whereas showing no presence of IgM antibodies and IgG-413 IU/ml with border avidity in 28 GA. On the second day after birth maternal serological tests were performed, obtaining anti-Toxo titers IgG 5489 IU/mL, IgM 14, 1 COI.

The first fetal ultrasonography examination (USG) performed in 18 GA did not show any abnormalities. The consecutive fetal cerebral USG at 28 GA revealed substantial bilateral ventriculomegaly. PCR amniotic fluid examination did not confirm *T. gondii* antigens. Isolated fetal defect in the form of increasing hydrocephalus was diagnosed, and the prophylaxis with Spiromycin was continued until the end of pregnancy. The above mentioned diagnosis resulted in premature delivery by caesarian section in 35 GA.

Female newborn, born from second pregnancy, first labor with birth weight 2510g (50 percentile), in moderate general condition, graded for 8,7,8 Apgar score. The physical examination confirmed the following abnormalities: increased muscle tone, periodical tetraplegia tremor, enlarged cranial diameter up to 35 cm (97 percentile; ear-to ear measurement about 21.5 cm), strained fonticulus anterior 3x4 cm, wide cranial sutures about 0,5 cm wide. The breath was irregular and quickened to 70/min with audible crackling above the lungs. Hepato-splenomegaly

DOI: 10.17772/gp/61990

palpable about 3 cm below arcus-costalis. Newborn reflexes were not entirely expressed. Newborn tests displayed accretion of IL-6 (53-96-163-234 pg/ml) with negative CRP and PCT serum levels and normal WBC counts, thromboctytopenia (71-84-79-1.0 thousand/mm3), anti-toxo IgG 1373 IU/ml, anti-toxo IgM 0.4 COI. In the first day of baby's life, cord blood and cerebro-spinal fluid PCR confirmed the presence of *Toxoplasma gondii*- DNA. Additionally, Rubeolla IgG 14 IU/ml and negative *CMV* was revealed in serology. Newborn's cerebral USG revealed active and extending hydrocephalus (LVR 0.67) with thin, almost impossible to measure cerebral stratum in occipital region, thickening up to 0.38 cm in temporal pole with multiple leucomalacia foci. Cerebro-spinal fluid collected by ventricular puncture high level of protein 1083 mg/dl and cytosis-21 (granulocytes-15, limfocytes-6) were marked. Interstitial pneumonia was observed radiologically. Presence of the fluid in pleura and peritoneal cavity was observed ultrasonographically. Additionally laboratory measurements indicated the rise of transaminases AspAT-189-78-27-30-31 IU/L; AlAT-29-19-10-11-15 IU/L, GGTP-721-369-158 IU/L, total bilirubin -11,81 – 7,20 – 3,42 mg% with bounded bilirubin – 0,79-2,30 - 1,48 mg%.

In ocular-ultrasonography (USG-A) microphthalmia was confirmed in both eyes (shortened axial length about 1.0 cm). The presence of persistent pupillary membrane, bilateral advanced posterior uveitis with dense exudate in vitreous (especially marked in the left eye, fig 1a), and numerous white-gray, fluffy, diffuse and probably active inflammation areas overlying vitritis in the right eye (fig 2a) were diagnosed in the indirect fundoscopy Ret-Cam II. Massive, dense exudate in the form of hyperechogenic masses was confirmed in USG-B left eye, (fig 1b) with substantial uveal thickening with irregular, hyperechogenic masses in USG-B right eye (fig 2b).

In USG-images further extension of cerebral fluid spaces and encephalotrophy were noticed (LVR index 0,79-0,9). Peritoneal shunt-chamber implementation was resigned due to the lack of features of active hydrocephalus and persistent encephalitis (CSF: cytosis – 12; granulocytes-8, limfocytes-4, protein- 903,40 mg/dl).

In the following ophthalmic examinations of both eyes slight improvement of local state was observed. In the left eye, small discrete limitation of exudate from retinal edge with visible hemorrhage foci were observed, fig 1c. In the right eye limitation of toxoplasmatic inflammation foci with their hyperpigmentation, the presence of scar proliferation extending temporarily from the optic disc to equator, optic disc developmental defect along with decrease of vitritis were disclosed, fig 2c.These lesions were confirmed in USG images (consecutively left eye fig.1d and right eye fig 2d).

Sulphadiazine, Daraprim, Calcium folinatum, Encorton were applied from the baby's second day of life. The follow–up serologic tests after 30 days revealed seroconversion anti-toxo IgM to 1,2 COI and the decrease of anti-toxo IgG to 369,1 IU/ml.

Discussion

Perinatal *T. gondii* contagiousness in range about 17%–80%, leads to congenital [8-14], severe form of toxoplasmosis [15,16]. Gestational age and baby's immunological maturity, placental pathology, parasitemia advancement in mother, virulence of the parasiteas well as the timing of anti-parasite therapy implementation should be mentioned as possible factors influencing mother-to-fetus toxoplasmosis transmission [17].

It has been shown, that in 90% of cases with congenital toxoplasmosis distant complications of the prevalent infection may appear. The most frequently they concern well oxidized organs simultanieusly nauturally isolated like blood-brain or blood-eye barrier making it difficult to reach immunological response to brain or eye-ball (about 15%) [15, 16, 18]. Toxoplasmatic central nervous system complications may include: epilepsy, mental retardation, speech impediment or various forms of cerebral palsy [19-23]. Ophthalmic changes might comprise: amblyopia, strabismus, uni-or bilateral blindness. In about 3-5% of these cases these lesions are irreversible.

This case report details congenital toxoplasmosis as a dramatic example of an ophthalmo-neurological birth defect despite anti-parasite prophylaxis used throughout pregnancy.

The main goal of primary infection treatment in the mother is the prevention of the transmission of the parasite from the mother to fetus and consecutively after infestation of the fetus, to minimize the severity of the disease. Currently, fetal diagnostics are based on PCR test and ultrasound. According to the guidelines for primary *T. gondii* infection in a pregnant woman, with negative PCR in amniotic fluid, Spiramycin treatment should be implemented in the shortest time possible. This medication is safe for the fetus without causing congenital defects, its activity is limited to the treatment of placenta inflammation [7,24]. Attention should be paid to the so called short " therapeutic window", which means that only the very early administration of Spiramycin, no later than three weeks from mothers seroconversion, reduces the risk of infection of the fetus [25].

It is possible that the lack of effect of the therapy was a result of the early transmission of the protozoa through the placenta before Spiramycin prevention was implemented. The low effectiveness of this medication, variable individual penetration into the fetus and the lack of ability to penetrate into the brain are also highlighted [26].

In case of ultrasound abnormalities in the fetus after 20 GA (hepatosplenomegaly, ascites, pleural effusion, hyperechgenic bowel, microcephalia, ventriculomegalia above15mm, calcification of the brain or liver, eye damage, intrauterine growth retardation) even withthe negative result of PCR of amniotic fluid, while suspecting intrauterine infection, it is recommended to intensify the treatment, which involves the use of combination therapy pyrimethamine with sulfadiazine and folinic acid [27].

Pirymetamin transmits through the placenta, therefore should not be applied in the first pregnancy trimester showing potential teratogenic activity [7]. Folinic acid is used in order to decrease the risk of hematologic complications (marrow suppression) connected to pirymetamin course.

The authors of the review have tried to explain the false negative result of amniocentesis. PCR tests are characterized by high sensitivity – 97, 4% and a specificity of 100% [28]. False-negative results are most often associated with early collection of amniotic fluid before infection of the fetus, therefore it is recommended to complete this test no earlier than 4 weeks after acute toxoplasmosis is diagnosed in them other. In the presented case, the delay was 10 weeks, the fetus was diagnosed with extension of the lateral ventricles due to toxoplasmatic inflammation. Therefore it must be assumed that in the amniotic

fluid were present parasites and in high concentrations, as evidenced by the severity of the clinical symptoms observed in the newborn. According to *Romand et al.* in mothers, in whom infection has taken place before 20 gestational weeks, *T. gondii* above 100 parasitoids per ml of amniotic fluid causes the highest risk for severe fetal complications (death or ventriculomegaly). In contrast lower value, below 100 parasitoids per ml, can characterize subclinical form of this infection or its mild course [29]. It should be recognized that this was a laboratory error, probably in DNA amplification. Negative PCR should not exclude fetal infection and therefore examination should be based on ultrasound every 2 weeks or NMR [30].

Systemic and local steroids (Encorton, Dexamethasone 0.1%) were applied for retino-choroidal lesions leading to limited local ophthalmic symptoms in the form of scars and fibrous forms in one eye, with the lack of any benefit in the other one. Noteworthy, the literature presents data on other alternative treatment possibilities for *T. gondii* that is intravitreous Dexamethason and Clindamycin as well as subconjunctival Clindamycin injections [31, 32].

According to the current knowledge, pregnancy abortion should be considered only in the case of lethal fetus defects [10]. Taking into account described case indicating that primary *T. gondii* infection can cause dramatic severe neuro-ophthalmic complications in infant, consequence, the authors highlight the need of multiple repetition of laboratory tests including fetal ultrasonography, supported with neurologic MR (magnetic resonance). These studies, in addition to PCR testing of amniotic fluid, even with its negative outcome, should be crucial for diagnosis.

Conclusion

It is worth underlining that the most appropriate period to perform amniocentesis and amniotic fluid test to detect DNA of the parasite is 15-20 hbd [33]. In case of a negative PCR results and full-blown ocular and multi-system toxoplasmosis the Spiramycin treatment efficacy in pregnant woman may be questionable. An effective alternative to Spiramycin to prevent in utero infection with *Toxoplasma gondii* may be azithromycin, a Category B drug used for treatment of *Chlamydia trachomatis* infections in pregnancy. Azithromycin has successfully treated *Toxoplasma gondii* in both an animal model and in humans with AIDS. After 21 weeks' gestation, treatment consists of sulfadiazine/pyrimethamine plus calcium folinate, alternating with spiramycin, to maximise efficacy while minimising toxicity. These agents are active against tachyzoites and are synergistic when used in combination in full-blown ocular and multi-system toxoplasmosis. A combination of Pyrimethamine (100 mg loading dose orally followed by 25 to 50 mg/day) plus Azithromycin (500 mg once daily) may also be tried. It should be remembered that, sulfadiazine and pirimethamine are contraindicated during the first trimester due to multiple side effects.

Consent:

A written informed consent was obtained from the patient's parent for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Acknowledgements:

We offer our sincere thanks to our colleagues from other departments and laboratories for their help and assistance in performing laboratory and microbiology tests.

Oświadczenie autorów:

1. Monika Modrzejewska – autor koncepcji i założeń pracy, przygotowanie i ostateczna weryfikacja manuskryptu – autor odpowiedzialny za manuskrypt.
2. JacekPatalan – współautor manuskryptu, wykonanie badań diagnostycznych, pomoc w uzyskaniu wyników badań.
3. Urszula Kulik – współautor tekstu pracy, przygotowanie piśmiennictwa, pomoc w przygotowaniu manuskryptu – autor zgłaszający manuskrypt.
4. Maria Beata Czeszyńska – pomoc w interpretacji wyników badań.

Źródło finansowania:

Praca nie była finansowana przez żadną instytucję naukowo-badawczą, stowarzyszenie ani inny podmiot, autorzy nie otrzymali żadnego grantu.

Konflikt interesów:

Autorzy nie zgłaszają konfliktu interesów oraz nie otrzymali żadnego wynagrodzenia związanego z powstawaniem pracy.

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