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Samileh Noorbakhsh *

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Research Article

Ocular Lesion Due To Congenital Infections with Cytomegalovirus, Toxoplasmosis: Diagnosis, Treatment And Follow-Up: A Prospective Study in Tehran, Iran

Mohammad Vafaee-Shahi[1], Samileh Noorbakhsh[2*], Leila Tahernia[3], Sarvenaz Ashouri[4].

[1] Pediatric growth and development research center, Iran University of Medical Sciences, Tehran, Iran.

[2] pediatric infectious diseases Department &Research center, Iran University of Medical Sciences. Tehran, Iran.

[3] University of Medical Sciences, Tehran, Iran.

[4] ENT and Head and Neck Research Center and Department, Hazrat Rasoul Akram Hospital, The Five Senses Health Institute, Iran University of Medical Sciences, Tehran.

Corresponding Author: Samileh Noorbakhsh, pediatric infectious diseases Department &Research center, Iran University of Medical Sciences. Tehran, Iran.

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Abstract

Intrauterine infections lead to involvement of various organs in fetus, including the eye. The aim of this study was to determine the frequency and clinical response of ocular lesions to specific drugs in infants with congenital Toxoplasma and cytomegalovirus infections. This historical cohort study was performed in the pediatric and ophthalmology department of Rasoul Akram Hospital in Tehran from October 2011 to November 2017. Patients included 78 infants with ocular involvement due to proven intrauterine infection (cataracts, glaucoma, and retinitis). Infants who did not undergo additional and diagnostic tests, eye examinations, and follow-up and did not receive effective treatment were excluded from the study. Three patients expired during the study. Finally, 37 patients (including 25 patients with cytomegalovirus and 12 patients with toxoplasmosis) were included to assess and the clinical response to ocular lesions was evaluated for one year. Of 12 cases with toxoplasmosis, 5 patients received complete treatment. Four patients had appropriate clinical responses. Of 25 patients with CMV, 18 patients received complete treatment and 9 patients had appropriate clinical responses.

It concluded that successful treatment will be obtained in near 80% of ocular toxoplasmosis. So anti toxoplasma treatment is recommended in all confirmed congenital cases. About 50% of CMV infected cases (with hearing loss, ocular involvement) might respond well to antiviral therapy. We recommend anti CMV treatment in young congenital CMV (<2 years old) but it is not indicated in CMV infected cases with severe brain involvement.

Keywords: cytomegalovirus; ocular disorders; t. gondii; intrauterine infections; infants

Running title: Ocular lesion in congenital infection; Cytomegalovirus, Toxoplasmosis

Introduction

Congenital or intrauterine infections are significantly important in all countries around the world in terms of prenatal control and postpartum diagnosis. Despite widespread use of vaccines to control common childhood infections, even in developed countries, infections such as cytomegalovirus, herpes, and other respiratory viruses or parasites such as toxoplasmosis cannot be prevented and may result in intrauterine infection syndrome in infants 1. The prevalence of cytomegalovirus in the world is between 40 and 100%. Toxoplasma is an important cause of intrauterine infection in neonates [2 , 3].

The prevalence of anti-toxoplasma antibodies varies in women of childbearing age in every country and even in different parts of a country [1-4]. The classic characteristics of congenital infections includes fever, hydrocephalus, microcephalus, hepatosplenomegaly, icter, seizure,

chorioretinitis, cerebral calcification, and increased protein and mononuclear poleocytosis in cerebrospinal fluid 5. It seems that the probability of developing congenital toxoplasmosis is much higher in Iran compared to the United States, about more than 60 to 80 times [6,7].

According to the studies conducted in Iran similar to other countries, cytomegalovirus is one of the most common intrauterine infections. The previous studies in Rasoul Akram hospital with the aim of neonatal screening had shown that cytomegalovirus was more common but had milder symptoms compared to other causes of intrauterine infections [8]. In Iran, toxoplasmosis screening has not yet been performed, while the incidence of toxoplasmosis is so high to be screened. Prenatal screening can help identify mothers who are susceptible to infection. Screening for antibodies enables early prevention of toxoplasmosis infection in which dietary habits and hygiene practices are clearly identified as risk factors [9]. Recent studies have shown that frequency of immunoglobulin G and M against toxoplasmosis were 44.1% and 1% respectively which was less than frequency in mothers. In all cases, the polymerase chain reaction (PCR) of the cerebrospinal fluid was negative. The most common symptoms of congenital infection were ocular (50%) and cerebral (50%) symptoms [10].

The purpose of this study was to determine the frequency and rate of response to treatment in ocular lesions in children with various types of intrauterine infections.

Methods:

The current historical cohort study was performed on all children aged up to 2 years referred to the clinic of ophthalmology department of the Rasoul akram Hospital in Tehran to diagnose and treat important ophthalmic problems from October 2011 to November 2017.

This study has adhered to the principles of Helsinki and has been approved by the ethics committee of the Infectious Diseases Research Center of Children affiliated with Iran University of Medical Sciences with code of 9321165001.Data from all individuals was also retained by the researchers. The all taken measures were after receiving informed consent from parents and all were completely necessary and very helpful for the diagnosis and treatment of referred patients.

Cases definition: Children with ocular lesions caused by intrauterine CMV and toxoplasmosis infections were included in this study.

All patients with eye lesions were followed regularly. Follow up sessions for at least a whole year were recorded in the file, and the results of ophthalmology examinations were recorded and finally evaluated. After this stage, all patients were referred to pediatrician in order to filling out the questionnaire, conducting additional evaluations according to the history and clinical examination, performing additional tests (if necessary) and finally study variables. The possible causes of ophthalmic lesions were identified. After diagnosing the site of involvement inside of the eye in each patient (retinitis, glaucoma, and cataract) for final diagnosis, determining the cause of ophthalmic lesions, examining other systemic problems in the child, all were referred to a pediatric clinic. Ultimately, in some patient's intrauterine infection was diagnosed.

Exclusion criteria: Patients who did not reach the final diagnosis, despite the available examinations, did not undergo additional and diagnostic tests and were excluded did from our study. Those who acted contrary to the ophthalmologist prescribed instructions for treatment or follow-up were excluded as well from the study.

Statistic: the frequency for the qualitative variables was expressed based on the mean and standard deviation and for the qualitative variables as the percentage. Comparison between quantitative variables was performed by Student's t-test and comparisons between qualitative variables were also performed using Chi-square test or Fisher's exact test. SPSS software, version 18 (IBM SPSS, Armonk, NY, USA) was used to analyze the data statistics. Levels less than 0.05 were considered significant.

Results:

Totally, between 78 cases of patients with the diagnosis of Intra uterine infection, 37 of them had ophthalmic lesions. Of total cases, 25patients were infected with CMV and 12 were infected with toxoplasmosis. Three patients expired meanwhile. Other patients did not receive antiviral treatment due to parental dissatisfaction, the severity of brain involvement and parental frustration with complete recovery. Due to the mentioned causes, medical treatment was limited to supportive measures such as cerebral shunting, treatment of heart problems and cochlear implants.

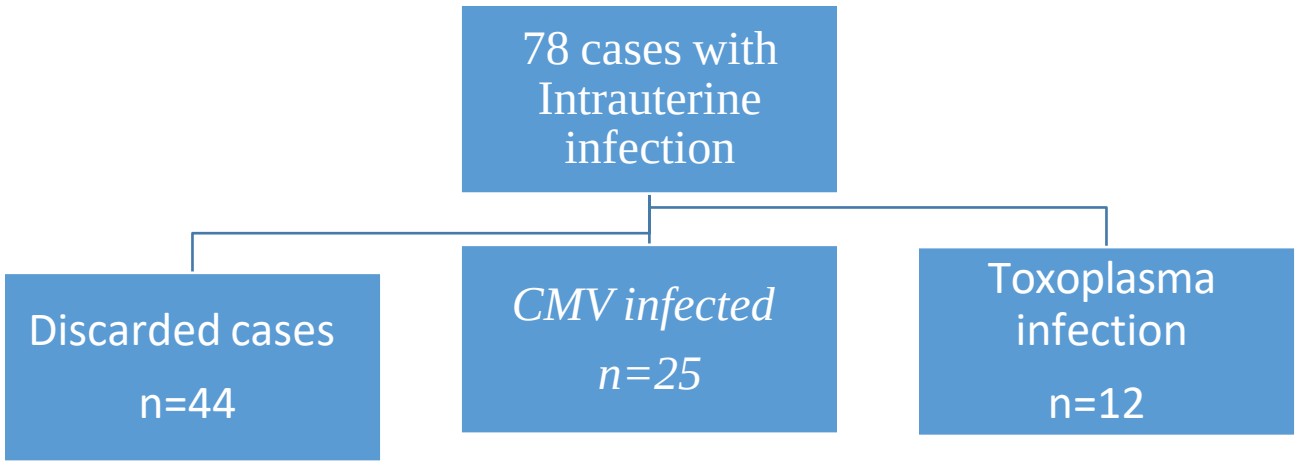

Figure-1: *selection of Cases with ocular disorders due to intrauterine infection*

Thirty-seven children were treated and examined for ophthalmic lesions resulted from intrauterine infection. Thirteen cases had specific treatment responses and 24 children did not respond to treatment. Of 12 children with ocular toxoplasmosis, only five patients continued their treatments, with four (80%) appropriate clinical response, but only one patient (20%) did not improve significantly despite treatment. Of 25 infants with cerebral involvement caused by congenital CMV infection, only 18 cases continued treatment. Totally 9 cases showed appropriate clinical

responses and remaining 9 patients did not improve significantly despite antiviral therapy. One case did not follow examining sessions after treatment. The lack of response to CMV treatment was mainly observed in patients with severe brain lesions from birth. The best response to treatment was reported in patients with hearing loss, ocular involvement and no brain involvement. Comparison between patients' clinical response to antiviral drugs based on sex and other variables could not be concluded due to the small number of cases. The ophthalmic involvement was not different between two groups of with and without clinical response (P = 0.3). The mean age of patients who had a good clinical response did not differ significantly from the unresponsive group. (4±1.5 compared to 4.2± 2.5 months) (P =0.7).

Discussion

In present study 25 patients with ocular lesion were infected with CMV and 12 were infected with toxoplasmosis. The ocular lesions responded well to specific treatment in 80% of toxoplasma cases and 50% of cytomegalovirus patients.

The unresponsive of CMV infection to antiviral therapy was generally observed in patients with severe brain damage at birth (due to severity and involvement in the early months of fetal period). The best response to treatment was detected in patients with hearing loss and ophthalmic lesions without cerebral involvement. The clinical response of CMV to specific drugs was not dependent on age of infants.

High CMV seroprevalance observed in Iranian pregnant women [9-11] On the other hand, congenital CMV infection has been one of the most common causes in infants suspected of having intrauterine infections not only in our center but also in other Iranian studies [12] .Karimina et al reported that from 1617 neonates born in Isfahan, only 8 cases at birth (49%) had a positive CMV-PCR (Polymerase chain reaction) in urine sample, that were mostly immature. In 3 patients, the clinical symptoms were temporary and resolved. In one case, a slight hearing loss was reported in the next follow-up [12].

In last decade results of studies for T Gondii infection determined the prevalence of T Gondii antibodies in Iranian population ranged between 24% to 57.7%. 13-15 Daryani et al. (2014) in a systematic review and meta-analysis studied the seroprevalence of T.Gondii in the Iranian general population in 35 studies 13. From of 35 reports, the overall seroprevalence rate of toxoplasmos among the general Iranian population was 39.3% (95% CI = 33.0%–45.7%). There was no significant difference in the seroprevalence rate between male and female patients. A significant linear trend of increasing overall prevalence by age was noted (P < 0.0001), a high seroprevalence in groups who have direct contact with cats, consume uncooked meat and raw fruits or vegetables, in farmers and Housewife, individuals who have a low level of education, and live in rural areas13. The epidemiological study of toxoplasma in pregnant women in Tehran showed that totally 34.3% of patients had previous immunity and 7% with recent infection ($^{+}$IgM), which did not differ from the prevalence of toxoplasma infection in voluntary blood donors in Iran. [15] About 35% of blood donors had positive IgG (31.4%) and IgM (2.74%) antibodies against T.Gondii. 15 In a recent meta-analysis study in Iran, it was shown that pregnant women accidentally had 41% antibodies against T.Gondii (+IgG :34% ;+ IgM :4%) [16] .The highest immunity (53%) observed in the southern parts and the lowest in the eastern regions (33%)

Indeed we observed previous (+IgG) and recent (+IgM) immunity to T Gondii in 34.7% and 7.1% of young pregnant women in in our centers , recent T Gondii infection (+IgM) observed in 9.8% of infants(<2y old) with intrauterine infection ; but previous immunity(+IgG) was higher in normal children .Like us, other Iranian studies determined this relation ,congenital toxoplasmosis caused by maternal infection during pregnancy have been identified as a common cause of intrauterine infection. In another prospective study, congenital toxoplasmosis was evaluated on umbilical cord blood of 270 newborns at birth. According to this study, +IgG and +IgM determined in 44% and 1.5% of neonates. Only 50% of +IgM cases had ocular symptoms and 50% had cerebral symptoms [17]. The positive anti-Toxoplasma IgM antibody in 2/ 2498 infants, 3 infants had borderline titers, which considered suspicious, and were retested for specific IgG after 18 months. They observed + IgG in 2 infants (also had +IgM). The positive genome of T.Gondii detected in 1 /2496 infants. The incidence of congenital toxoplasmosis was estimated near 0.08% without significant differences for epidemiological factors and congenital infection [17].

So, congenital toxoplasmosis can be prevented by the treatment of Active T.Gondii infection in pregnant women [17].

Conclusion

Successful treatment will be obtained in near 80% of ocular toxoplasmosis, so anti toxoplasma treatment is recommended in all confirmed cases. About 50% of CMV infected cases (with hearing loss, ocular involvement) might respond well to antiviral therapy, we recommend anti CMV treatment in young cases (<2 years old) but it is not indicated in CMV infected cases with severe brain involvement.

Declarations:

Ethics approval and consent to participate:

This study was accredited by Ethical Committee of Iran University of Medical Sciences. Helsinki Declaration was respected across the study and the informed consent form was signed by the parents.

Competing interests

The authors declare no conflict of interest in preparing this study.

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All authors confirm Consent for publication

All authors confirm Availability of data and materials

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