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Review / Derleme

Congenital toxoplasmosis

Konjenital toksoplazmozis

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Abstract

Congenital toxoplasmosis is a disease that can be seen worldwide. Fetus, newborn and infants with congenital Toxoplasma infection are at risk in terms of infection-related complications. As the gestational age increases, infection development risk of the fetus increases but the severity of the disease decreases. Most of the fetuses that are infected at the early stages of pregnancy and can't be treated are lost in utero or in the neonatal period or severe neurologic and ophthalmologic sequel develops. Diagnosis must be made to differentiate the toxoplasmosis from the other intrauterine infections that present similar findings in the newborns and other causes of the retinal lesions. It is suggested to initiate the treatment in newborns diagnosed prenatally with congenital toxoplasmosis regardless of whether the mothers received treatment during pregnancy and to apply antiparasitic treatment in patients with confirmed diagnosis and strongly suspicious diagnosis.

Keywords: Congenital toxoplasmosis, diagnosis.

Özet

Konjenital toxoplazmosiz yagın görülebilen bir hastalıktır. Konjenital toxoplasma enfeksiyonuna maruz kalmış fetus, yenidoğan ve infantlar, komplikasyonlar yönünden risk altındadırlar. Gebelik haftası arttıkca, hastalığın şiddeti azalmasına ragmen, fetusda enfeksiyon gelişme riski artar. Erken gebelik haftalında enfekte olmuş fetusların çoğunda, tedavi edilemeyenlerde, inutero veya yenidoğan döneminde tedavide geç kalındığı durumlara beyinde ve gözlerde sekeller gelişir. Toxoplazmosiz diğer intrauterine enfeksiyonlaradan ayırdedilmelidir. Yenidoğanda tedaviye başlamak için, gebeliği sırasında, süpheli ve kesin tanıyla tedavi alıp almamasına bakılmaksızın, konjenital topzoplazmosisin prenatal tanısının konması önerilmektedir.

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Anahtar sözcükler: Konjenital toksoplazmozis,tanı

Introduction

Toxoplasma gondii is an intracellular protozoon which can infect humans and animals. Toxoplasma infection is typically asymptomatic in immunocompetent hosts. Moreover, a serious disease table may emerge in case of immunosuppression or congenital infection. Fetus, newborn and infants with congenital Toxoplasma infection are at risk in terms of infection-related complications. Toxoplasma has a biphasic lifecycle as sexual cycle, which occurs only in cats, and asexual cycle, which also occurs in other animals and humans. Cats get infected by eating the oocystes in the earth or the tissue cyst forms in the animals they hunt. Replication occurs in the cat's intestine, oocyste form emerges, is excreted and becomes infectious after 24 hours. Millions of oocystes can be excreted on daily basis until three weeks during the primary infection. Asexual cycle of the Toxoplasma replication begins in people who consume food contaminated with the cat scat containing Toxoplasma oocyste. Oocystes are torn as the characteristic of the acute stage of the infection, sporozoites are released and then become tachyzoites. Tachyzoites are spread over the whole body through blood stream and lymphatics. In case of sufficient immune responses, tachyzoites take the form of bradyzoites and form the tissue cysts. Bradyzoites are the sign of the infection's presence at the chronic stage and they may exist during the whole life of the person.

Epidemiology

Congenital toxoplasmosis is a disease that can be seen worldwide. Prevalence of the primary toxoplasma infection in women at the reproductive age differs geographically (1-3). Among the places where T. gondii infection is observed, the highest rates have been reported in Europe, Central America, Brazil and Central Africa (1). According to the data obtained in our country, seropositivity exists in people above the age of 40 by 60% and it was discovered during the examinations on pregnant women that IgG positivity existed by 34-70% and this rate was between 37-84% in women who had a miscarriage, stillbirth and premature birth (4-7).

Pathogenesis

Three of oocyste, bradyzoite and tachyzoite forms of T. gondii can cause a disease in people (8). Congenital infection typically occurs through the transplacental transmission of the tachyzoites after the primary infection of the mother during pregnancy; however, it may rarely develop in a pregnant woman with weak immunity after reactivation (2, 9). The probability of the feturs to get infected during the acute maternal infection changes depending on the gestational age when the maternal infection occurred (10). As the gestational age increases, infection development risk of the fetus increases but the severity of the disease decreases (3, 11).

Most of the fetuses that are infected at the early stages of pregnancy and can't be treated are lost in utero or in the neonatal period or severe neurologic and ophthalmologic sequel develops (12). In infections that emerge in the second or third trimester, slight or subclinical disease table is encountered at birth. Severity of the congenital toxoplasmosis

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also depends on the immune system of the host and the virulence of the T. gondii strain besides the gestational age (2, 13, 14).

Clinical Findings

Congenital toxoplasmosis has a large clinical spectrum. Classic triad of the congenital toxoplasmosis consists of chorioretinitis, hydrocephalia and intracranial calcifications. However, classic triad is observed in less than 10% of the patients (15). Most of the newborns are asymptomatic.

Clinical presentation has 4 forms (2): subclinical infection, severe disease in the neonatal period, slight or severe disease in the first a few months of life, sequel formation or recurrence of the undiagnosed infection in the infantile period, childhood or adolescence (generally ocular).

Subclinical infection

No findings can be detected in the routine physical examination of 70-90% of the newborns with congenital toxoplasmosis (4, 16, 17). When the suspicion of congenital infection is very strong, it is suggested to conduct more specific tests such as the examination of the cerebrospinal fluid, detailed examination and screening of the central nervous system (9, 18).

Disease table

Symptoms and findings of congenital toxoplasmosis are seen at birth only by 10-30% (9, 18). Symptomatic infection generally emerges as a result of the primary maternal infection that develops in the first trimester. Clinical findings are too many and nonspecific. These include chorioretinitis (86%), abnormal cerebrospinal fluid findings (63%), anemia (57%), convulsion (41%), intracranial calcification (37%), jaundice (43%), splenomegaly (41%), hepatomegaly (41%), lymphadenopathy (31%) and pneumonia (27%).

Chorioretinitis

Chorioretinitis is the most frequently encountered table in the clinic (19). Incidence of the new-onset retinal lesions in untreated children reaches 90%. Focal necrotized retinitis is the typical lesion (20). Findings like microphthalmia, strabismus, cataract and nystagmus may also accompany. Loss of vision, retinal detachment, neovascularization of the retina and optic nerve, cataract, glaucoma and iris changes are among the complications of toxoplasma chorioretinitis. Differential diagnosis of the chorioretinitis in infants includes the other chorioretinitis infections that progress with the retinal lesion (cytomegalovirus, herpes simplex virus, rubella, varicella, syphilis), chorioretinitis anomalies and congenital hypertrophy of the retinal pigment epithelium.

Differential Diagnosis

Diagnosis must be made to differentiate the toxoplasmosis from the other intrauterine infections that present similar findings in the newborns and other causes of the retinal lesions. Differential diagnoses include rubella, cytomegalovirus, syphilis, congenital lymphatic choriomeningitis virus syndrome, congenital retinal anomalies and congenital

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hypertrophy of the retinal pigment epithelium (2). Methods of serology, ophthalmologic examination and central nervous system screening can help for the differential diagnosis.

Assessment and Diagnosis

Early diagnosis is important for the early onset and effectiveness of the treatment. Maternal serology and newborn screening must be applied or the suspected cases with clinical findings must be confirmed with laboratory tests.

Clinical Suspicion

Congenital toxoplasmosis must be suspected in babies who are born from women that went through primary T. gondii infection during pregnancy, babies who are born from women that were immunosuppressive during their pregnancy after having T. gondii infection, babies who have clinical findings leading to infection (intracranial calcifications, chorioretinitis, inexplicable mononuclear cerebrospinal fluid pleocytosis or increased cerebrospinal fluid protein) and babies whose toxoplasma IgM tests have been found positive. Additional clinical, laboratory and screening methods must be applied to all the newborns with the possibility of congenital toxoplasmosis due to the difficulties in the interpretation of the serologic tests in the newborns.

Clinical assessment

Assessment must be made for the newborn with the suspicion of congenital toxoplasmosis including complete physical examination, T. gondii serology, ophthalmologic and neurologic examinations, anamnesis and serology of the mother. Diagnosis is generally made by bringing clinical and laboratory findings together.

Eye examination

Chorioretinitis can be seen as the single clinical finding. It is suggested that the retinal examination of the newborn be made by a specialized ophthalmologist.

Neurologic examination

Central nervous system abnormalities may be the single finding of the congenital toxoplasmosis. Central nervous system involvement can be observed as increased cerebrospinal fluid protein or mononuclear cerebrospinal fluid pleocytosis. Isolation of the toxoplasma-specific IgM or T. gondii itself in the cerebrospinal fluid will confirm the diagnosis. Cranial screening is performed to assess the focal brain lesions or hydrocephalia. Unenhanced computed tomography is preferred to magnetic resonance imaging, because it is quick and cheaper and generally there is no need for sedation. Abnormalities in the neurologic screening may include one or more intracranial calcifications, hydrocephalia (characteristically secondary to periaquaductal involvement) and cortical atrophy.

Hearing examination

All the newborns with the suspicion of congenital toxoplasmosis must be examined for hearing. Early intervention can be performed with the early diagnosis of the hearing problems and the response to treatment becomes better.

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Laboratory assessment

Serology

Diagnosis of the congenital toxoplasmosis is often made through serology in newborns, but interpretation of the serologic tests can be complicated; in such cases, it will be useful for the patient to consult an infectious diseases specialist. The possibility of the dependency of the newborn's anti-toxoplasma lgGs on the past or current infection in mother, loss of the fetal IgM antibody before birth, possible effect of the prenatal treatment on the serologic profile, late appearance of the newborn's antibody response and low-level and positive observation of the antibodies in the newborn who wasn't affected in the period right after birth because of the placental escape of the maternal IgM and IgA antibodies can be counted among the situations that cause complication. Blood samples of both the newborn and the mother must be examined for an accurate serologic assessment. IgG and IgM are positive in a woman who had acute toxoplasma infection and is immunologically normal. Toxoplasma-specific IgM may be seen in the first a few days of life or appear at different times after birth (depending on the timing of the maternal infection) (3). Accordingly, a negative Toxoplasma-specific IgM result doesn't eliminate the congenital infection. IgM antibodies generally emerge 10 days after the infection and become negative within 3-4 months, but sometimes, they may not be detected for years.

If the IgM result is negative or suspicious in a newborn, IgA and IgE ELISA must be considered (21-23). In congenital toxoplasmosis, IgA or IgE are more sensitive than IgM but their specifities are not so good (2, 9). Repeating the tests may help the diagnosis when the newborn is 10 days old. IgM and IgA titers increase quickly in an uninfected newborn (Positive ones at a low level depending on the placental escape), but they remain positive during the periods changing between weeks and months in an intrauterine infected newborn (9, 24). When the results at onset are suspicious, multiple serologic tests must be conducted during the first year. Toxoplasma-IgG titers transited transplacentally on the maternal basis decrease down to undetectable levels during the periods changing between 6 weeks and 12 months (9). On the contrary, toxoplasma-specific IgG levels remain high in newborns with congenital infection almost for one year.

Demonstration of T. gondii

In clinical samples, demonstration of T. gondii or T. gondii nucleic acids can help with the confirmation of the diagnosis. However, these methods are less used because they are not easily accessible and tissue samples are required.

Lumbar puncture, complete blood count, liver function tests, serum creatinine and urine analysis, researching the glucose-6-phosphate dehydrogenase insufficiency (Before using sulfadiazine, sulfamerazine or sulfamethazine in the treatment) are the other suggested laboratory procedures.

Treatment

Serious sequels, especially chorioretinitis have been demonstrated in children, who were diagnosed with congenital toxoplasmosis and weren't treated, by up to 90% (25, 26). It is suggested to initiate the treatment in newborns diagnosed prenatally with congenital

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toxoplasmosis regardless of whether the mothers received treatment during pregnancy and to apply antiparasitic treatment in patients with confirmed diagnosis and strongly suspicious diagnosis (27).

As the treatment option, pyrimethamine, sulfadiazine and folinic acid combination is frequently suggested. No complete agreement has been reached on the treatment doses and duration yet, but the following suggestions are made frequently:

Continuation of 2 mg/kg pyrimethamine (maximum 50 mg) once a day for two days, then 1 mg/kg (maximum 25 mg) once a day for six months, and then 1 mg/kg (maximum 25 mg) every other day until the completion of 1 treatment year,

Continuation of sulfadiazine giving its total dose of 100 mg/kg/day in two equal parts for one year,

Continuation of folinic acid in 10 mg doses three times a week during the pyrimethamine treatment and continuation for one more week after the pyrimethamine treatment (3, 9, 28-30).

With the one-year combination treatment, significant decrease has been observed in newborns with clinical toxoplasmosis findings when compared to the patients who didn't receive treatment in case of the incidence of long-term sequels and new-onset ocular disease or who were treated in a shorter time (27, 31). Glucocorticoids (prednisone 0.5 mg twice a day) can be added into the treatment in case of the existence of protein> 1 mg/dL in the cerebrospinal fluid or active chorioretinitis which threatens vision (27). Clindamycin can be used in newborns with the development of allergy against sulfadiazine (32). Skin rash is the most encountered allergic reaction that depends on the sulfadiazine; leucopenia, which is a serious complication, is rarely observed. Main side effect of pyrimethamine is neutropenia and it generally appears after an accompanying viral infection; it is often healed by increasing the folinic acid dose.

Disease Follow-Up

Serologic follow-up is suggested in patients with congenital toxoplasmosis until up to 18 months. Physical examination, hearing examination and especially ophthalmologic examination must be performed periodically. After the completion of the treatment, toxoplasma-specific IgG and IgM levels must be checked every 3-6 months.

Disease Prevention

There are no vaccines that have been developed to prevent toxoplasmosis yet. Transmission risk can be decreased with activities such as avoiding raw meat consumption, washing the hands and kitchen stuff after any contact with raw meat, consuming vegetables and fruit after washing them properly due to the risk of contamination with oocystes and avoiding any contact with cats and their leftovers.

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