THE CONSEQUENCES OF THE CONGENITAL INFECTION WITH *TOXOPLASMA GONDII* ON THE OFFSPRING

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Abstract. Statistically, 90% of the pregnant women who are also infected with *Toxoplasma gondii* do not show any symptoms. During the parasitemia that is consecutive to the primary site of infection, the parasite disseminates to the placenta through blood, so the infection can be transmitted to the fetus through the placenta. Most of the times, the routine examination of the newborns, does not show the usual signs of congenital toxoplasmosis. The study aims to determine the frequency of cases of congenital toxoplasmosis, to assess the health of babies and children from mothers with acute infection, and also to illustrate the consequences of the infection with *Toxoplasma gondii* on the offspring and to correlate them with the gestational age. This prospective study was conducted on a total sample of 152 pregnant women who were hospitalized and investigated in “Elena Doamna” Iasi Clinic of Obstetrics and Gynaecology. In the period of time between 2001 and 2014 we identified a number of 108 children (69%) showing a damage of the central nervous system (CNS) and 44 children (28%) with generalized manifestation of the disease. The mortality rate recorded in these children was 12%, without any significant differences between those with CNS damage and those with generalized disease ($p<0.05$). About 85% of the survivors developed mental retardation, 75% convulsions, spasticity, paralysis and 50% impaired vision. More than 80% of these children have an IQ < 70, most of them showing convulsions and severely impaired vision. The cutaneous manifestations of congenital toxoplasmosis include: rash, petechiae, bruising or massive hemorrhage secondary to thrombocytopenia. Also present in other congenital infections, the consequences on the offspring will be all the more severe as the transmission of the parasite toxoplasma infection from the pregnant woman to the foetus occurs earlier in pregnancy.

INTRODUCTION

Toxoplasmosis, a parasitic disease that often shows no symptoms in the mother, has important repercussions on the baby and is more frequent than it is statistically estimated. The data published in literature show a level of sero-prevalence of 30-40%, higher in occupational exposure categorized as risk of infection with this parasite (Abbasi, 2003; Ministerul Sănătății, România, 2011).
Because of its extent and distribution, its frequency in the general population and also because of the severity of manifestations in adults and especially in the newborns, because of the difficulties in getting a diagnosis of certainty, toxoplasmosis is a matter of real importance in the work of health units.

Table 1. Serological diagnosis of congenital infection with *T. gondii* in the newborn (Remington, 1990)

Infant age	Examination performed	Remarks
First day of life	Serological testing to determine specific IgM, with cord blood testing and peripheral blood confirmatory study. Comparison of the immunological maternal and cord levels.	IgM-ISAGA and DS-IgM- ELISA testing is positive in 70% of the cases with congenital toxoplasmosis. RIF-IgM testing is positive in just 25% of the cases with congenital infection. The difference is significant if titer in the cord blood is four times higher than the one in maternal blood.
15 days	IgM testing in the child’s blood.	The positive result in the cord blood that turns into a negative result for the peripheral blood harvested afterwards suggests the possibility of contamination with maternal blood. The negative result in the cord blood that turns into a positive result for the peripheral blood harvested afterwards suggests the transmission of the infection shortly before birth.
1,2,4,6,8	Comparison of immune levels in	An increase or the maintaining of a steady level proves the

Infant age	Examination performed	Remarks
months	recent samples in relation to the previous samples.	synthesis of specific antibodies by the child's body. A decrease in the antibodies level suggests the absence of their synthesis due to the absence of infection or the reduced antigenic stimulus, proving the efficiency of the treatment (the immune level monitoring is useful in assessing the effectiveness of the treatment).

The transplacental transmission rate of *T. gondii* increases in relation with the age of the pregnancy at the moment when the primo-infection occurred (Rădulescu, 2000; Silveira, 2003).
The speciality literature cites an average of 14% - 17% cases of congenital transmission from the total number of cases with acute infection in pregnancy for the first trimester of pregnancy. The percentage increases in the second trimester to 25%, in the third trimester it goes over 59%, and in the last three weeks of pregnancy the transmission of the parasite occurs in over 90% of the cases with acute infection. (Couvreur, 1983; Lupea, 2000).
In congenital toxoplasmosis, the parasite shows an obvious tropism for the central nervous system and for the ocular system, regardless of other systemic sites of infection, more or less obvious. This preferential localization does not seem to result from an organo-tropism, but from a weaker strength of the brain and ocular tissue. The importance of lesions at these levels is amplified by the reduced capacity for regeneration of these tissues compared with the remarkable regenerative capacity of the other tissues in the body.
Rarely, *T. gondii* can be located in the lungs, causing an interstitial pneumonia; in the myocardium, causing necrosis and inflammation; the parasite can persist as a parasitic cyst. At pericardium level it causes acute, then chronic pericarditis; in the kidney, it induces glomerulo-nephritis by antigen-antibody immune complexes. When the parasite is located in the liver or spleen, the organism reacts by hepatosplenomegaly. Other locations mentions, rarely met, are: cortico-suprarenal, pancreatic, in the digestive tract, thyroid, thymus, ovaries or testes, in teguments, skeletal muscles and bone marrow (Popoviciu, 1993; Rădulescu 2000, Stănilă, 1996; Stamatin, 2003).
There can also be some endocrinological abnormalities by affecting the hypothalamus, pituitary gland or peripheral glands. Studies mention and describe myxedema, persistent hypernatremia with Vasopressin-Sensitive Diabetes Insipidus, with no polyuria or polydipsia, precocious puberty, and hypopituitarism (Lloyd, 2013).

MATERIAL AND METHODS

The study was performed on 152 children, coming from mothers hospitalized and investigated in "Elena Doamna"Iasi Clinic of Obstetrics and Gynecology, with a definite diagnosis of neurological impairment (n=108) and systemic impairment (n=44), following an intra-uterine infection with *T.gondii*.

Table 2. Signs and symptoms that appear after the diagnosis in the children with acute congenital toxoplasmosis

Signs and symptoms	Frequency of events (%) for the subjects with	
	Neurological disease	Systemic disease
Newborns	108 subjects	44 subjects
Chorioretinitis	102 (94%)	29 (66%)
Pathologic LCR	59 (55%)	37(84%)
Anaemia	55 (51%)	34 (77%)
Convulsions	54 (50%)	8 (18%)
Cerebral calcifications	54 (50%)	2 (4%)
Icterus	31 (29%)	35 (80%)
Fever	27 (25%)	34 (77%)
Splenomegaly	23 (21%)	40 (90%)
Lymphadenopathy	18 (17%)	30 (68%)
Hepatomegaly	18 (17%)	34 (77%)
Microcephaly	14 (13%)	0
Vomiting	17 (16%)	2 (48%)
Diarrhea	7 (6%)	11 (25%)
Cataract	5 (5 %)	0
Glaucoma	2 (2 %)	0

Signs and symptoms	Frequency of events (%) for the subjects with	
	Neurological disease	Systemic disease
Newborns	108 subjects	44 subjects
Microphtalmia	2 (2 %)	0
Eosinophilia	6 (4 %)	8 (18 %)
Pathologic bleeding	3 (3 %)	8 (18 %)
Hypothermia	2 (2 %)	9 (20 %)
Optic nerve atrophy	2 (2 %)	0
Cutaneous rash	1 (1 %)	11 (25%)
Pneumonia	0	18 (41%)

The macroscopic examination reveals a pale and edematous placenta, with an increased volume. Microscopic examination shows free or cystic parasites that are located in the villous, especially in the stroma, trophoblast, in the endothelial cells of the chorionic vessels and Wharton’s jelly, and also in the decidua. Villous lesions are mononuclear inflammatory infiltrate type, histiocytic and with giant cells. Chorionic villi edematous degeneration is relatively frequent.

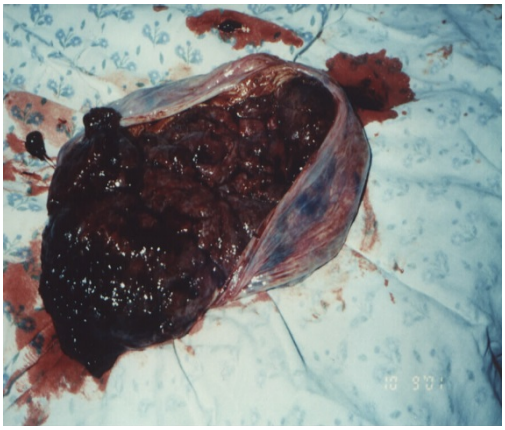

Fig. 1. Placenta. Macroscopic aspect post-infection with *Toxoplasma gondii* (“Elena Doamna” Iaşi Hospital collection)

Ocular fundus examination may also reveal a papillitis that is secondary to the adjacent inflammation or a papilledema that is consecutive with the hydrocephalus. Extended lesions can cause the central atrophy of the retina. The parasites with an intracellular location can be found in all choroid and retina layers. The choroid appears thickened, with hyperemia, infiltrated. When the choroid is affected, it frequently causes damage to Bruch’s membrane and proliferation of connective tissue in the sub retinal space. As a result, the retina and the choroid will be fixed to one another by a scar.

RESULTS AND DISCUSSIONS

Congenital infection was suspected, most often following a serological screening of pregnant women with acute infection with *T. gondii*. 21 cases were discovered (13.8%) as having severe congenital toxoplasmosis involving the central nervous system, the visual system and also showing general systemic lesions. 56.7% of them manifested a mild form of the disease, with a normal general clinical examination except retinal scarring and intracranial calcifications.

If the foetus gets infected with *T. gondii* when the pregnancy age is 10–24 weeks, the consequences will be extremely serious. They will be: congenital malformations, severe impairment of the central nervous system, systemic damage, and lead in most cases to spontaneous abortion, intrauterine death, prematurity and dysmaturity, severe neonatal infections

with plurivisceral touch, hemorrhagic syndrome, icterus, hepatosplenomegaly, encephalopathies with lethal ending in 5–15% of the cases, or to progressive sequelae of a fetal disease with hydro- or microcephaly, intracranial calcifications and chorioretinitis.

Systemic damage. From the total number of children with a disease that was clinically manifested at birth, 25-50% are born before term, getting a low Apgar score. This group includes those children with intrauterine growth retardation and instability in temperature control. Other systemic manifestations include: lymphadenopathy, hepatosplenomegaly, myocarditis, nephritic syndrome, vomiting, diarrhea and eating disorders. There can be some transparent metaphyseal bands and irregularities of the provisional calcification line of the epiphyseal plate without periosteal reaction in the ribs, vertebrae and femur. (Ambulatory Child Health, 2000).

The **central nervous system** impairment is manifested by diffuse or focal meningoencephalitis, accompanied by tissue necrosis, microglial nodules, perivascular mononuclear inflammatory infiltrates.

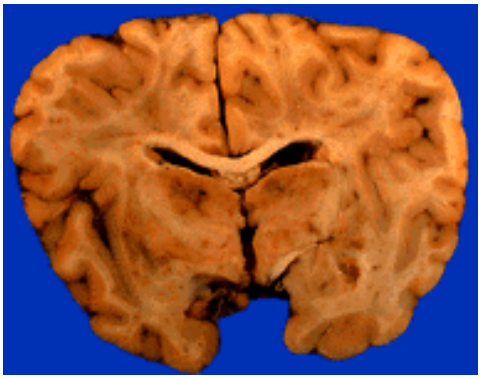

Fig. 2. **Toxoplasmic encephalitis.** Multiple outbreaks of hemorrhagic necrosis and cerebral edema (www.gtmer.ch)

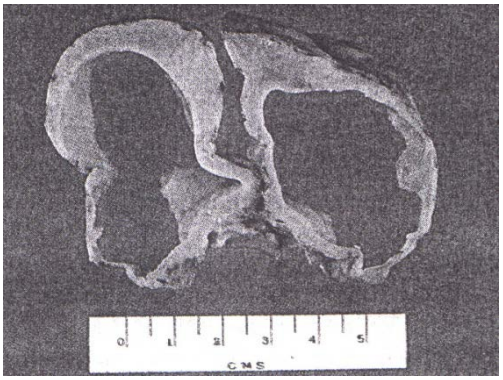

Fig. 3. C**ongenital toxoplasmosis**. Ventricular dilatation postencephalitic fasciitis (Umberto de Girolami, 1999)

The neurological m**anifestations** of congenital toxoplasmosis vary from massive acute encephalopathy to subtle neurological syndromes. Toxoplasmosis must be considered the cause of an undiagnosed neurological disease in children under one year old, especially if retinal lesions are present.
Hydrocephaly can be the only manifestation of congenital toxoplasmosis and it can exist either compensated, or requiring the execution of a shunt during the perinatal period or later.

The eyes are affected mainly by chorioretinitis. It is estimated that both in the U.S.A. and in Europe, *T. gondii* is the most common etiologic agent of chorioretinitis, causing about 35% of the cases (Brezin, 2003; Pinon, 2003).
Most children with congenital toxoplasmosis will develop subsequent episodes of chorioretinitis, if not treated. (Leblebicioglu, 2002).

Toxoplasmic chorioretinitis is, most frequently, the consequence of a congenital infection and very rarely of an acquired one (1%); the maximum frequency is attained between 20-40 years old and very rarely over 50 years old.

In **toxoplasmic chorioretinitis** the lesion is characterized by the appearance of macular plaque of chorioretinitis, usually for both eyes. The atrophic oval plaque has net pigmented slightly protruding margins. The centre is white, and the sclera is visible because of the chorioretinal necrosis. The parasite is present in the lesion and the more numerous it is, the more severe the lesion. Occasionally it can be observed without an associated inflammatory reaction, in apparently normal areas of the retina, at the periphery of inflammatory foci, alone or in groups, free inside the cell or as a cyst and rarely in the choroid. It was described as being located in the tissues of the optic nerve and optic nerve head. More rarely met in the vitreous body, the hemorrhages can be accompanied by signs connected to the appearance of strabismus, nystagmus, the paralysis of the VIth pair of cranial muscles and optic atrophy.

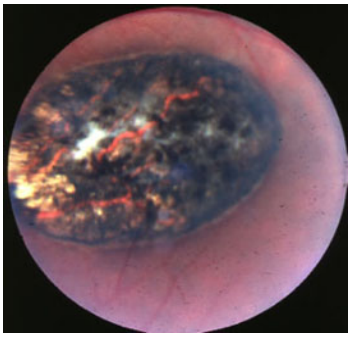

Fig. 4. Chorioretinitis in congenital toxoplasmosis (www.opt.indiana.edu/.../Text3beta.html)

Liver damage/impairment, manifested through icterus, or **lung impairment** manifested through interstitial pneumonia, can be present, and so can the secondary **edemas** of myocarditis or the nephritic syndrome. Icterus and conjugated hyperbilirubinemia can persist for months (Lloyd, 2013).
The severity of the consequences in the congenital infection decreases gradually if it occurred further from the 26^{th} week of pregnancy. Thus, if the transplacental infection occurs in the last trimester of pregnancy, the newborn can show a subclinical form of infection at birth, which can be overlooked. In the absence of an adequate treatment that is applied immediately, the infection will develop mild forms of the disease in 85% of cases, immediately afterwards or in childhood. The sequelae can be: *ocular* (isolated microphtalmia, strabismus, episodes of chorioretinitis with different degrees of vision impairment, up to blindness), *neurological* (hypotonia, transitory drowsiness, delays in the physical and mental development, *hepatic* (icterus at an early age of a few weeks).

CONCLUSIONS

The prevalent signs and symptoms for the children with congenital toxoplasmosis were: staturo-ponderal hypotrophy, convulsive syndrome, microcephaly, psychomotor retardation of different degrees, ophthalmologic changes (mainly chorioretinitis).

In the infections that occur shortly before conception and in the first 10 weeks of pregnancy, the congenital transmission rate of *T. gondii* to the offspring is very low, below 1%. If the infection occurred, this will result in over 90% of the cases in a pregnancy stopped in evolution, death and miscarriage.

There is therefore an inversely proportional relationship between the incidence of fetal infection and the severity of the destruction caused by it, in relation to the gestational age.

It must be mentioned that once the placental infection occurs, the placenta will stay infected throughout pregnancy, even after overcoming the phase of toxoplasmic parasitemia.

About 2/3 of the cases with congenital toxoplasmosis do not show the known symptoms, as there are oligosymptomatic forms of the disease, and often the diagnosis of toxoplasmosis is generally established in the chronic phases of the disease, unaccompanied by high or increasing titers of antibodies. That is why, a large scale serologic screening programme should be considered in order to prevent and decrease the severe consequences met in congenital toxoplasmosis.

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