CLINICAL CONTEXT

Congenital Toxoplasmosis

Congenital toxoplasmosis is a particular form of toxoplasmosis contracted by the unborn child during the mother's pregnancy. It can cause serious clinical manifestations in the fetus or at birth (Saadatnia & Golkar, 2012). Congenital toxoplasmosis is responsible for 190,000 cases per year worldwide, with an estimated global impact of 1,200,000 Disability Adjusted Life Years (DALYs) (Torgerson & Mastroiacovo, 2013).

Almost all congenital toxoplasmosis occur as a result of a primary infection in the mother during pregnancy, whether the infection is symptomatic or not (Gangneux & Dardé, 2012).

Congenital toxoplasmosis can also occur as a result of reactivation of toxoplasmosis in an immunocompromised mother, or more rarely if the mother's primary infection occurred shortly before pregnancy, particularly in the case of symptomatic toxoplasmosis in the mother or, even more rarely, in the case of a second infection with a strain that is more virulent than the first strain that infected the mother previously (Simon et al., 2020; Maldonado & Read, 2017).

The clinical presentation of congenital toxoplasmosis varies greatly depending on several factors, particularly the stage of pregnancy at which the infection occurred: the earlier in pregnancy the infection occurs, the lower the likelihood of infection, but the more severe the clinical presentation is (Wallon et al., 2013).

Furthermore, the establishment of a close follow-up diagnosis of pregnant women and the initiation of early treatment of the mother would be a protective factor, reducing both the frequency and severity of congenital toxoplasmosis. Although no randomized trials could be performed to prove the usefulness of such a treatment in a formal way, many studies, including large cohort studies(Mandelbrot et al., 2018, Wallon et al., 2013), have shown the effectiveness of a treatment, and an increasing number of teams and scholarly associations agree with this position (Pleyer et al., 2019; El Bissati et al., 2018; Avelino et al., 2014; Peyron et al., 2019; McLeod et al., 2016). In addition, as treatment was more effective in these studies when initiated within 8 weeks of infection, regular diagnosis of seronegative women in pregnancy is also recommended (Mandelbrot, 2020, Montoya, 2018, Picone et al., 2020). This is even an obligation in some countries, such as France or Austria (see also the paragraph on seroconversion monitoring in the toxoplasmosis page). The implementation of prenatal monitoring of toxoplasmosis is considered to be a beneficial technique in terms of public health: the cost-benefit ratio is very much in favor of this approach (Prusa et al., 2017 ; Bobic et al., 2019), as is cost-effectiveness (Binquet et al., 2019).

The main forms described in the context of congenital toxoplasmosis are :

Asymptomatic congenital toxoplasmosis

Congenital ocular toxoplasmosis

Cerebral congenital toxoplasmosis, multi-visceral, in-utero deaths or non-viable births.

ASYMPTOMATIC CONGENITAL TOXOPLASMOSIS

The asymptomatic form is the form most often described in France because of the strict monitoring of pregnancies and newborns of mothers who have seroconverted and the treatments offered during pregnancy, however this is not the case in countries that do not practice prenatal screening, such as the United States (Peyron et al., 2017).

The diagnosis of choice for congenital toxoplasmosis is the performance of amniotic fluid PCR during pregnancy. This technique is extremely specific. Despite its very high sensitivity, however, it can present false negative results due to too early sampling, before the toxoplasmas are implanted in the amniotic fluid, or due to treatment which can reduce the parasite load below the detection limit. In the absence of amniotic fluid PCR, and because of transmission of maternal immunoglobulins at birth and through breastfeeding, which can lead to false-positive results, the positive serology of the child alone is not sufficient to make the diagnosis of congenital toxoplasmosis. In this case, the diagnosis is based on evidence of IgG, IgM or IgA synthesis by the child through the existence of a different immune profile between mother and child demonstrating the child's synthesis of antibodies against antigens not recognized by the mother (L'Ollivier et al., 2012; Villard et al., 2016).

The diagnosis of exclusion of congenital toxoplasmosis is long and is based on the disappearance of anti-toxoplasmosis IgG in children in the first year of life. It remains recommended to maintain anti-toxoplasmosis treatment for 3 to 12 months after birth in case of suspicion of asymptomatic form, as there is a risk of delayed ocular form. Also, treating the mother seems to reduce performances of all diagnostic tests in the newborn, serological as well as inoculation or PCR (Guegan et al., 2021). Therefore, these children should also have a reinforced ophthalmologic follow-up until adulthood (Konstantinovic et al., 2019).

CONGENITAL OCULAR TOXOPLASMOSIS

It consists of ocular toxoplasmosis following a congenital infection. It can be diagnosed at birth, or it may be diagnosed following reactivation later in life. The damage is more severe and more frequent in the case of parasites with an atypical genotype, such as those found in South America. (Maenz et al., 2014; Huang et al., 2018).

This is the most common congenital condition and, unlike the other symptomatic forms, it is often found in infections in the late stages of pregnancy (Wallon et al., 2013). For this reason, it is recommended that children who have had congenital toxoplasmosis be followed up for life (Wallon et al., 2014).

In a very large number of cases, pathognomonic lesions of ocular toxoplasmosis, as observed on fundus examination, allow the diagnosis on the basis of the clinic, but certain atypical forms require the use of biological diagnostic tools (Garweg, 2016).

The diagnosis of ocular toxoplasmosis cannot be made by isolated toxoplasmic serology: most toxoplasmic infections do not cause ocular injury. Therefore, serological techniques must demonstrate intraocular antibody synthesis.

The diagnosis of ocular toxoplasmosis can be made by observation of lesions in the fundus, by PCR in the aqueous humor, by looking for local antibody synthesis by Goldmann-Witmer or Candolfi coefficients using Elisa techniques, or by comparison of IgG or IgA immune profiles by Western Blot (Greigert et al., 2019).

In France, the Haute Autorité de Santé (HAS) recommends the use of profile comparison by immunoblot, combined with DNA and Goldmann-Witmer coefficient search techniques, for the diagnosis of ocular toxoplasmosis, whether congenital or not (Argumentaire HAS, 2017).

CEREBRAL CONGENITAL TOXOPLASMOSIS, MULTI-VISCERAL, IN-UTERO DEATHS OR NON-VIABLE BIRTHS

Those are the most severe forms of congenital toxoplasmosis, found in a context of infection most often in the first trimester, and with a poor prognosis.

Brain damage can range from harmless intracranial calcifications to massive hydrocephalus with destruction of a large part of the brain and major psychomotor delays. Cerebral toxoplasmosis can also be responsible for epilepsy.

Disseminated forms correspond to a dissemination of the toxoplasm in the whole organism of the foetus or newborn, generally associated with major brain damage. The parasite also causes lung and heart failure, most often resulting in fetal death in-utero, miscarriage or death in the first hours or days of life.

Diagnosis is based on imaging and clinical evidence, in the context of proven congenital toxoplasmosis. In the absence of maternal serological follow-up, ultrasound may be the first warning sign of severe congenital toxoplasmosis.

Severe forms are much less observed in countries that have implemented prenatal screening. Otherwise, treatment at birth sometimes makes it possible to limit the damage even if the risk of major lesions remains very high (McLeod et al., 2004; Peyron et al., 2017).

DIAGNOSIS OF CONGENITAL TOXOPLASMOSIS

The diagnosis of congenital toxoplasmosis must be made in the event of seroconversion of the mother during pregnancy, positive serology for the newborn in the case of neonatal screening, or, in the case of severe forms, in the event of suspicion on ultrasound or in the event of ocular toxoplasmosis at birth.

In case of maternal seroconversion or indicative ultrasound, diagnosis can be made by PCR on amniotic fluid. This technique is very sensitive, but false negatives are possible if the sample is taken too close to the infection or if maternal treatment has been initiated (Villard et al., 2016).

At birth, or if amniotic fluid PCR cannot be performed, the diagnosis can be based on PCR on cord blood or amniotic fluid, testing for IgM and IgA in the child and then confirming them 2 weeks later, or on a profile comparison by Western Blot in IgG and IgM (Maldonado & Read, 2017; Villard et al., 2016).

The Western Blot technique by comparison of immune profiles, developed in the 1980s, has since been widely used to respond to a diagnosis of suspected congenital toxoplasmosis (Remington et al., 1985).

In France, the Haute Autorité de Santé (HAS) recommends the use of profile comparison by immunoblot, combined with techniques to search for IgM and possibly IgA and DNA, for the diagnosis of toxoplasmosis at birth or during the first months of life (Argumentaire HAS, 2017).

To meet the demand, we have developed a reliable test for comparing immune profiles, based on the Western Blot technique, using natural T. gondii antigens obtained from in vivo cultures: the Toxoplasma WB IgG IgM test.

If the tests are negative, it is recommended that the child be followed up monthly until IgG is negative, as some forms can be diagnosed late. Any stabilization or increase in IgG levels, or any persistence after 12 months should be interpreted as congenital toxoplasmosis (Dard et al., 2016; Pomares & Montoya, 2016).

SCIENTIFIC REFERENCES

Mandelbrot L. Congenital toxoplasmosis: What is the evidence for chemoprophylaxis to prevent fetal infection?. Prenat Diagn. 2020;10.1002/pd.5758.

Mathis T, Beccat S, Sève P, Peyron F, Wallon M, Kodjikian L. Comparison of immunoblotting (IgA and IgG) and the Goldmann-Witmer coefficient for diagnosis of ocular toxoplasmosis in immunocompetent patients. 2018; Br J Ophthalmol. 102(10):1454-1458.

Murat JB, Hidalgo HF, Brenier-Pinchart MP, Pelloux H. Human toxoplasmosis: which biological diagnostic tests are best suited to which clinical situations?. 2013; Expert Rev Anti Infect Ther. 11(9):943-956.

Stillwaggon E, Carrier CS, Sautter M, McLeod R. Maternal serologic screening to prevent congenital toxoplasmosis: a decision-analytic economic model. 2011; PLoS Negl Trop Dis. 5(9):e1333.

Villard O, Cimon B, L'Ollivier C, Fricker-Hidalgo H, Godineau N, Houze S, et al. Help in the Choice of Automated or Semiautomated Immunoassays for Serological Diagnosis of Toxoplasmosis: Evaluation of Nine Immunoassays by the French National Reference Center for Toxoplasmosis. 2016; J Clin Microbiol. 54(12):3034-3042.

TOXOPLASMA Western Blot IgG IgM

TOXOPLASMA WB IgG-IgM is an immunoblot assay for the Comparison of Immunological Profiles (CIP-WB) for IgG and IgM that is intended to diagnose:

Congenital toxoplasmosis at birth (D0): CIP-WB G+M between maternal blood and cord blood.

Congenital toxoplasmosis in post-natal monitoring (D+N): CIP-WB G+M between the cord blood at D0 and the child's blood at D+N.

Ocular toxoplasmosis: CIP-WB IgG between the patient's serum and aqueous humor.

The comparison of pairs of IgG and IgM strips allows to show the presence of additional bands on the strip which indicates the local antibody synthesis and infection with Toxoplasma.

Each kit is composed of sensitized and precut strips and the ready-to-use liquid reagents.