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IgG Avidity Test to Discriminate between Acute and Chronic Toxoplasmosis

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Abstract

Serodiagnosis of toxoplasmosis is usually achieved by the detection of IgG and IgM against *Toxoplasma gondii*. Routinely the detection of IgM antibodies is an acute phase indicator, but in the case of this disease, this isotype can persist even after years of this initial phase of infection, which represents many disadvantages during the diagnosis early of the congenital transmission, that occurs when an infected pregnant woman transmits the parasite to her unborn baby. Numerous researchers have conducted studies to detect recent infections that arise in an unapparent way, without clinical symptoms (asymptomatic), in newborns or fetus infected by congenital route, which due to the lack of administration of a rapid and timely chemotherapeutic treatment can present severe pathological damages, and even, trigger in the death. Serological tests can present difficulties in differentiating acute cases of chronic infections. The IgG avidity test has been developed to distinguish between latent acute and infections in pregnant women who present a mixture of IgG isotypes and IgM anti-*T. gondii*. It is an important additional tool that saves time and money in the diagnosis of infections in women during pregnancy, as well as favors an accurate clinical management because it allows determining the toxoplasmosis phase safely and effectively.

Introduction

During pregnancy it is important to know the time when the infection by *T. gondii* occur, because the probability of congenital transmission can be determined, in order to begin treatment, as well as placing in strict prenatal care with appropriate care measures to the mother and the baby that is in the process of development. Acute maternal toxoplasmosis acquired during the first trimester of pregnancy often causes high rates of mortality and morbidity in developing fetuses, due to the appearance of serious pathologies, such as severe neurological damages, or fetal death [1].

Infection acquired later, within the second or third trimester, is more likely to be asymptomatic at birth leading usually to much less severe injury of the newborn and later of the child [2]. A rapid and accurate diagnosis is required in order to start the relatively efficient anti-parasitic treatment [3]. The presence of IgM during toxoplasmosis has the disadvantage that it can persist for years, much more than what is normally described, so it cannot be used as an acute phase marker [4]. This is a problem because as previously determined, the transmission to fetus occurs predominantly in women who acquire acute infection during pregnancy [5]. This drawback has led several authors to develop an assay to detect the infection phase of toxoplasmosis and thus lead the way to clinical monitoring of patients, called IgG avidity test, a method described by Hedman in 1989, whose principle is based on the differences found in the forces of the union that originated in the interaction antigen-antibody, which allows to discriminate between recent infection (acute phase) and infection acquired long ago (chronic phase). At the beginning of the infection are produced mainly IgG anti-T.gondii antibodies of low avidity, however, in the chronic phase show a high avidity [6].

The IgG avidity ELISA test consists of an immunoenzymatic assay in which a destabilizing agent of hydrogen bridges, such as urea and thiocyanate, is used to dissociate the binding between the specific IgG and the antigen, in such a way that in recent infections, low avidity IgGs are almost totally dissociated from the antigen-antibody complex, while high-avidity chronic infections they remain mostly bound to *T. gondii* antigens (Figure 1).

The methodology is explained in more detail as follows: the microtiter plates coated with toxoplasma antigens and then blocked are washed 3 times with PBS plus 0.05% Tween 20 (PBST). The serum samples were diluted 1/200 and added (100 µl / well) in 2 rows of a plate (row A and row B), after incubation for 45 min at 37°C; row B is washed 3 times with PBST, and row A is washed 3 times with the modified PBST buffer containing 6 M urea and a fourth time with PBST.

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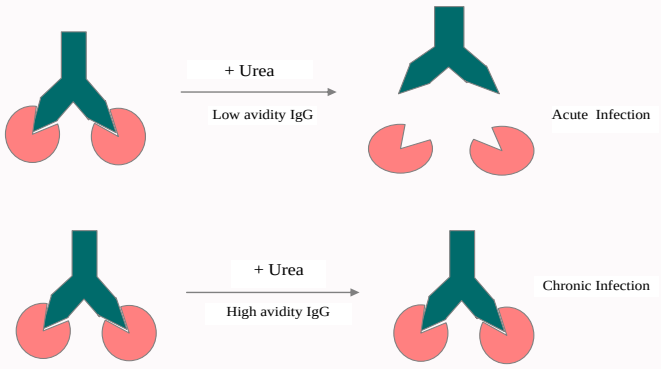

Figure 1: Diagram showing the characteristics of a test of low avidity IgG and another of high avidity IgG.

Anti-human IgG conjugated with horseradish peroxidase (HRP) is added at the dilution of 1/1000 in PBST. After incubation and washing, the chromogenic substrate, o-Phenylenediamine (OPD) is added. The reaction was stopped by addition of sulfuric acid 20%. The absorbance (Abs) was read with an automated ELISA reader at 492 nm. Avidity index (AI) expressed in porcentage was calculated as the result of Abs of wells washed with PBS-urea (U +), divided by the Abs of wells washed with PBST (U-), and multiplied by 100, based on the formula; AI = Abs (U +) / Abs (U-) × 100. High avidity (AI ≥ 60%) means that toxoplasma infection was acquired before 3 months ago, whereas borderline avidity (50% < AI < 60%) means infection at an indeterminate period, and low avidity (AI ≤ 50%) means that the infection was acquired within the last 3 months [7,8].

Studys of Assay IgG Avidity

Villard, et al. (2013) [9] have evaluated four assays, from Architect Toxo IgG Avidity (Abbott), Vidas Toxo IgG Avidity (bioMérieux), Platelia Toxo IgG Avidity (Bio-Rad), and Liaison Toxo IgG Avidity II (DiaSorin), which are the most widely used in French biology laboratories and in reference laboratories abroad. These fully automated assays are based on the exclusion of acute infection, with previous expert advice reporting good performance of the assays. The Architect assay, which employs recombinant antigens, provided the best performance for detecting latent infection in the presence of persistent IgM. This means that the use of recombinant antigens for toxoplasmosis assays could be extended in the future, considering that the type of antigen used in antibody recognition is crucial. For example, IgGs against antigens recognized early (i.e., GRA7, GRA8, and ROP1) mature significantly earlier than those directed against later antigens (i.e., SAG1 and MAG1) [10]. This study shows that the avidity test provides a rapid means for identifying latent toxoplasma infection in pregnant women who show IgG and IgM anti-toxoplasma antibodies on initial testing during pregnancy. This assay presents some drawbacks, since in the evaluation of some immune compromised patients and treated for toxoplasmosis does not present conclusive results. For this reason, in these peculiar cases, where optimal diagnostic performance is required, it is essential to carry out several tests together, such as serological, culture-based, and PCR techniques.

Berredjem, et al. (2017) evaluated the contribution of IgG avidity and PCR for the early diagnosis of toxoplasmosis in pregnant women from the North-Eastern region of Algeria [11]. A total of 143 sera samples of women pregnant were evaluated; the results obtained were: 57 seropositive: 30 (52.6%) were IgG + / IgM- and 27 (43.8%) IgG + / IgM +; IgA antibodies positive in 7 (12.2%) cases. IgG avidity was low in 9 samples suggesting an acute infection; while 3 presented an intermediate avidity. The DNA of toxoplasma was present in 9 samples with low avidity and was negative for the intermediate avidity cases, determined by PCR. In conclusion, the IgG avidity is a useful tool to evaluated serum samples from pregnant women with positive antibodies IgM anti-toxoplasma. A negative PCR result together with positive IgG / IgM indicates past infection, which would be excellent in cases of serological samples that present ambiguous or doubtful results, particularly in the presence of samples with intermediate avidity. The most striking results of this investigation show that the high titers of anti-toxoplasma antibodies, low avidity and presence of DNA of the parasite are related to the presence of acute toxoplasmosis. These types of studies are important because they avoid difficult moments for the patient, such as stress due to a large number of exams, loss of time, money and administration of unnecessary treatment.

Conclusions

The conventional serology to detect IgG and IgM antibodies against T. gondii allows determining the presence of infection, but does not provide evidence on the infection phase of toxoplasmosis, nor the time that has passed since the parasite has entered the human.

This is extremely important in the case of pregnant women, to give them a better quality of life in their gestation period and to minimize the pathological damages that occur in the newborn, through an efficient and rapid diagnosis, which favors the administration of chemotherapy. Depending on the phase of the toxoplasmosis in which the individual is found. For this reason, many researchers have devoted themselves to the task of developing serological methods with particular characteristics that allow knowing if there is a recent infection or a long time ago that has started. As a result of these studies has been obtained the IgG avidity test, which is based on the principle that after the initial antigenic exposure, the IgG antibodies produced during the acute phase bind weakly to the antigen (low avidity), with the progress of the immune response there is an increase in the maturation of the response of IgG antibodies and the strength of the antigen-antibody interaction rise progressively during weeks or months (high avidity). Through avidity IgG assays positive pregnant women should be considered in order to assess risks of miscarriage or congenital transmission. It was shown that combination of the sensitivity of IgM test for toxoplasma and the specificity of the IgG avidity test is the best tool to obtain the time of infection, is now widely used to differentiate between acute and chronic T. gondii

infections hence the great benefits of conducting these tests.

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