


Onset of Ocular Complications in Congenital Toxoplasmosis Associated with Immunoglobulin M Antibodies to Toxoplasma gondii

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Four patients with congenital toxoplasmosis serologically diagnosed by the Sabin-Feldman test (SFT) and the IgM-indirect fluorescent antibody test (IgM-IFAT) in the first year of life presented with eye disease between the age of 21 months and ten years. Repeated serological testing revealed increasing levels of specific antibodies as measured by the SFT. IgM antibodies to Toxoplasma gondii were detected in all four patients by the immunosorbent agglutination assay, in two by the IgM-IFAT and in three by the IgM-indirect haemagglutination test. Findings suggest that specific IgM antibodies reappear at the time of reactivation of congenital toxoplasmosis later in life, or possibly persist for an extraordinary long period (up to ten years).

Congenital toxoplasmosis is a serious disease with potentially severe consequences. Although clearly manifest in only 10% of cases in the neonatal period (1), almost all children born with subclinical congenital infection with Toxoplasma gondii will develop adverse ocular or neurologic sequelae (2). Furthermore, ocular disease occurs in 50% of all congenitally infected infants by the age of 18 (3). The fact that sequelae can largely be prevented by timely administration of specific therapy (1, 2, 4) emphasizes the importance of early diagnosis. If however there is failure to establish the diagnosis of congenital toxoplasmosis in the neonate, it becomes crucial to identify the lesions of the eye, central nervous system or other organs which might be sequelae of congenital infection with Toxoplasma gondii.

The diagnosis is mainly based on serological evidence, which in the neonate is often complicated by fetomaternal transmission of specific IgG antibodies. On the other hand, specific IgM antibodies present in the neonate’s circulation clearly indicate intrauterine infection. Of the tests at present available for the detection

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of specific IgM antibodies to *Toxoplasma gondii*, the immunosorbent agglutination assay (ISAgA) (5) has been shown to have the highest sensitivity (6-8) and to be the most reliable, and thus appears to be the reference test for congenital toxoplasmosis.

After the introduction of the ISAgA in our laboratory, various groups of patients were tested, including those who had previously been diagnosed as having latent congenital toxoplasmosis and later reported with eye disease. IgM antibodies to *Toxoplasma gondii* were detected in some of them. The purpose of this paper is to present results showing the occurrence of specific IgM antibodies at the time of reactivation of the disease later in life.

**Materials and Methods.** The study group consisted of four patients (3 females and 1 male) with congenital toxoplasmosis diagnosed serologically some time in the first year of life, who later at ages between 21 months and ten years presented with eye disease characteristic for ocular complications of congenital toxoplasmosis.

Antibodies to *Toxoplasma gondii* were detected by the Sabin-Feldman dye test (SFT) (9) modified by Desmonts (10) to a test of lysis (TL). Parasites of a virulent RH strain were propagated by serial intraperitoneal passages in Swiss albino mice. Sera were diluted 1:10, 1:100 and 1:1000, dilutions in between or higher being made if necessary. The results are expressed as the final serum dilutions at which more than 50 % of the parasites had been lysed (titre).

Specific IgM antibodies were detected by the IgM-indirect fluorescent antibody test (IgM-IFAT) (11), the IgM-indirect haemagglutination test (IgM-IHAT) (12) and the ISAgA (5). All reagents were obtained commercially (bio Mérieux, France). For the IgM-IFAT, sera were diluted 1:2, 1:10, 1:50 etc. A titre of 1:10 was considered positive in infants in the first year of life, whereas in older infants the first finding considered positive was a titre of 1:50. For the IgM-IHAT, sera were diluted 1:20, 1:40, 1:80 etc; a titre of 1:40 was considered to be the first positive finding. The ISAgA results are expressed in values ranging from 0 to 12, where values of 0–5 represent negative reactions, 6–8 borderline reactions and 9–12 positive reactions.

If two or more serum samples from the same patient were analysed in one test, these were run in parallel. Between tests sera were stored at -20°C.

**Results and Discussion.** Four patients serologically diagnosed in the first year of life as having latent congenital toxoplasmosis presented with eye disease (chorioretinitis in three patients and panuveitis in one patient) at ages between 21 months and ten years. All clinical and serological findings are shown in Table 1. The diagnosis of congenital toxoplasmosis had originally been established on the basis of the finding of persistent SFT titres up to the age of seven to twelve months and specific IgM antibodies, as detected by the IgM-IFAT. These infants presented with unspecific symptomatology, presumably because of which none of them received any specific therapy for toxoplasmosis, despite positive serological tests. Later, at the time of manifestation of eye disease, serological tests showed active toxoplasmosis, i.e. increases in specific antibody titres in the SFT were registered in all three patients in which sequential sera were available, while the single serum sample obtained from patient no. 1 showed a substantially higher titre than expected in latent toxoplasmosis. Specific IgM antibodies were detected in two patients by the IgM-IFAT, in three by the IgM-IHAT and in all four by the ISAgA. However, high values in the ISAgA were obtained in the first serum sample taken shortly after the onset of symptoms, at the time at which specific IgM antibodies were detected in only one patient by the IgM-IFAT and in none by the IgM-IHAT (Table 1).

Specific IgM antibodies, as a marker of primary infection, are thought to persist in the serum several months after the onset of infectious disease. However, their detection depends very much on the sensitivity of the method used. Thus, in infants congenitally infected with *Toxoplasma gondii*, specific IgM antibodies can be detected by the IgM-IFAT for a period of up to 4.5 ± 0.96 months after birth (13), in comparison to up to ten months by the IgM-enzyme immunoassay (14) and up to 18 months by the ISAgA (8). In the latent congenital toxoplasmosis patients presented in this paper, high ISAgA values were obtained at the age of 21 months to ten years. Specific IgM antibodies were detected by the IgM-IFAT in the first year of life (ISAgA had not been introduced at that time), which turned negative at a certain point, and later became positive again in two patients at the time of clinical reactivation of the disease. These two positive IgM-IFAT results, and also the high ISAgA values obtained in all four patients at the time of the onset of ocular disease (at the age of 21 months, 3, 7 and 10 years respectively), might indicate new production of specific IgM antibodies and their reappearance in the serum. Reappearance of IgM antibodies to *Toxoplasma gondii* has occasionally been suggested. Thiermann and Stagno (15) reported that specific IgM antibodies can occur in cases of chronic toxoplasmosis for as long as several months. They associated the reappearance of specific IgM antibodies with localized exacer-