Revision of the positive predictive value of IgM anti-*Toxoplasma* antibodies as an index of recent infection

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SUMMARY

The severity of congenital *Toxoplasma gondii* infection underlines the need for a precise diagnosis of acute infection during pregnancy. The search for specific IgM has been widely used for this purpose, but their possible early disappearance or persistence over time limits their meaning. In order to estimate the positive predictive value of anti-*Toxoplasma* IgM testing, we made an epidemiological analysis of the presence of anti-*Toxoplasma* IgG and IgM using ELISA in 4786 subjects attending the Hospital of Legnano in 2004-2005: 1360 seen for a clinical check-up and 3426 pregnant women for serological screening. In relation to IgG avidity, the positive predictive value of IgM was 45.98% (95% CI: 35.51-56.45) as a whole: this increased to 83.87% (95% CI: 70.92-96.82) in the patients with a highly positive test for IgM, but decreased to 9.52% (95% CI: 0.00-22.07) in pregnant women with a weakly positive test for IgM. Our results indicate that a highly positive IgM value in patients can be a good index of recent infection, but its poor predictive value in pregnant women underlines the need for additional tests with a follow-up if necessary.

KEY WORDS: IgM anti-*Toxoplasma*, Predictive value, Toxoplasmosis

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INTRODUCTION

Toxoplasmosis is found throughout the world but its country prevalence varies depending on socio-economic conditions. Published data concerning the seroprevalence of anti-*Toxoplasma* IgG specific antibodies range from 10% in Norway (Jenum *et al*., 1998), to 10-18% in Great Britain (Ades *et al.*, 1993; Allain *et al.*, 1998), 15% in the USA (Jones *et al.*, 2003), 19-29% in Spain (Gutierrez-Zufiaurre *et al*., 2004; Munoz Batet *et al*., 2004), 24% in Greece (Diza *et al*., 2005), 14-26% in Sweden (Petersson *et al*., 2000), 27% in Denmark (Lebech *et al*., 1993), and 55% in France (Ancelle *et al.*, 1996). The infection is generally benign in immunocompetent individuals, in whom only 10% of the infections are symptomatic (McCabe *et al*., 1987) but more severe and at times lethal in immunocompromised subjects. Congenital infection is particularly important as its clinical features include hydrocephalus, microcephaly, intracranial calcifications, chorioretinitis, strabismus, blindness, epilepsy, psychomotor or mental retardation, petechia due to thrombocytopenia, and anemia. However, none of the signs described in newborns with congenital disease is pathognomic for toxoplasmosis, but can be mimicked by congenital infection with other pathogens. Children with subclinical manifestations at birth can develop symptoms of overt toxoplasmosis later.

It has been estimated that congenital toxoplasmosis affects approximately 1-10/10000 newborn

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babies in Europe (Gilbert, 2000), and so it is particularly important to make a correct diagnosis of acute infection during pregnancy.
The available tests include a specific search for IgM antibodies to identify acute or recent infections.
These can be found approximately 14 days after infection (Joynson and Guy, 2001) and disappear some months later (Remington *et al.*, 2001; Joynson and Guy, 2001), but the possibility of their early disappearance or persistence over time (even for as long 3-4 years) limits their meaning (Gras *et al.*, 2004; Sequela, 1982). A search can also lead to false positive results due to the presence of natural antibodies, rheumatoid factor, or antinuclear antibodies, and studies have reported 1.3% false positive results during pregnancy in countries with a low prevalence of infection (Jenum *et al.*, 1998).
Moreover, commercial tests for anti-*Toxoplasma* IgM have been criticised because of their poor specificity: one recent study recorded a false positive rate of 88.6% with a specificity of 11.4% and positive predictive value of 6% (Garry *et al.*, 2005).
In the case of IgM positivity, characterising the infection therefore requires other tests such as differential agglutination (AC/HS) (Dannemann *et al.*, 1990) or the detection of IgG (Sabin and Feldman, 1948; Dannemann *et al.*, 1990), IgA (Stepick-Biek *et al.*, 1990) or IgE (Wong *et al.*, 1993), or their combination (Liesenfeld *et al.*, 1996; Montoya and Remington, 1995), and determining IgG avidity has proved to be particularly helpful in discriminating recent and more remote previous infections (Lappalainen *et al.*, 1993; Lecolier and Pucheu, 1993; Stronati *et al.*, 1996).
However, such tests are not always used and physicians do not always know the meaning and limitations of a positive IgM test: for example, although the American Food and Drug Administration (FDA) issued a warning about commercial IgM tests in 1997 (Public Health Service US, 1997), only 12% of obstetricians/gynaecologists in the USA knew about the possibility of false positive results in 1999 (Jones *et al.*, 2001).
The aim of this study was to estimate the presence of anti-*Toxoplasma* IgM in the population residing in the area of Legnano and calculate the positive predictive value of an IgM test in patients attending hospital for a clinical check-up and in pregnant women undergoing serological screening.

MATERIALS AND METHODS

In 2004 and 2005, the Microbiology Unit of the Hospital of Legnano received the blood samples of 4786 subjects: 1360 patients seen for a clinical check-up (537 males and 823 females aged between one month and 91 years), and 3426 pregnant women aged 15-44 years undergoing serological screening under the terms of a 1998 Italian Health Ministry decree (Official Gazzette No. 245 of 20/10/98). All of the samples were ELISA tested for anti-*Toxoplasma* IgG (ETI-TOXOK-G-PLUS DiaSorin, Saluggia, Italy) and IgM antibodies (ETI-TOXOK-M reverse PLUS, DiaSorin, Saluggia, Italy). The cut-off value for IgG was 15 IU/mL.
In relation to IgM, the samples whose absorbance was equal to or more than the "cut-off control" absorbance were considered positive. The ELISA IgM-positive samples were also tested by means of IgM ELFA (VIDAS Toxo IgM, BioMérieux, Lione, France). The samples with an index of ≥0.65 were considered positive, and those with an index of 0.55-0.65 were considered borderline.
Whenever possible, the ELISA IgM-positive samples were also assessed for IgG anti-*Toxoplasma* avidity (VIDAS Toxo IgG Avidity, BioMérieux, Lione, France).
Rheumatoid factor was also looked for (Arthri-Slidex, BioMérieux, Lione, France).
The data were statistically analysed using the χ^2 test and Fisher's exact test.

RESULTS

Of the 4786 subjects, 1312 (27.41%) were positive for anti-*Toxoplasma* IgG and 98 were positive for anti-*Toxoplasma* IgM antibodies, one of whom was also positive for rheumatoid factor and excluded from the subsequent analyses; the remaining 97 (2.03%) were negative (Table 1).
Five hundred and seventy-five of the 1360 patients (42.28%) were positive for IgG and 55 (4.04%) positive for IgM at ELISA; among the pregnant women, the corresponding figures were

737 (21.51%) and 42 (1.23%) (Table 1). The differences between these subgroups were statistically significant (p<0.01).
In terms of gender, 227 of the IgG-positive patients were men (42.27%) and 348 were women (42.28%); the ELISA IgM-positive patients consisted of 19 men (3.54%) and 36 women (4.37%) (Table 2). These differences were not statistically significant.
The samples of the 97 subjects who were positive for anti-*Toxoplasma* IgM were divided into two groups on the basis of the ratio of the absorbance of the sample to the absorbance of the "cut off control" (47 highly positive with a ratio of ≥1.75 (group A) and 50 weakly positive with a ratio of between 1 and 1.75 (group B)), and retested using the ELFA test for IgM. A total of 75 of these samples (77.32%) were ELFA positive or borderline: 46/47 (97.87%) in group A and 29/50 (58.00%) in group B, a statistically significant between-group difference (p<0.01) (Table 3). Table 3 shows that there was no significant difference between the patients and pregnant women considered separately, although the difference between A and B remained significant (p<0.01).
IgG avidity could be determined in 87 samples: 34 of the 47 group A (72.34%) and six of the 40 group B samples (15.00%) showed low or borderline avidity, and 13/47 (27.66%) and 34/40 (85.00%) high avidity (Table 4). The difference between group A and B was statistically significant (p<0.01). When the data concerning the patients and pregnant women were considered separately (Table 4), the differences between A and B remained statistically significant (p<0.01).
Avidity was not determined in ten cases because the search for IgG was negative; all of the samples were weakly IgM positive at ELISA. Seven of these cases (two ELFA positive or borderline, and five ELFA negative) were followed up: three remained weakly positive for IgM at ELISA for 1-9 months, whereas IgM disappeared within 2-7 months in four cases; IgG never appeared dur-

TABLE 1 - *Seroprevalence of IgG and IgM anti-Toxoplasma antibodies in patients and pregnant women (years 2004-2005).*

	Anti-toxoplasma antibodies			
Elisa	*Patients*	*Pregnant women*	*P*	*Total*
IgG positive	575 (42.28%) 95% CI: 39.65-44.91	737 (21.51%) 95% CI: 20.13-22.89	<0.01	1312 (27.41%) 95% CI: 26.15-28.67
IgM positive	55 (4.04%) 95% CI: 2.99-5.09	42 (1.23%) 95% CI: 0.86-1.60	<0.01	97 (2.03%) 95% CI: 1.63-2.43
Total	1360	3426		4786

TABLE 2 - *Seroprevalence of IgG and IgM anti-Toxoplasma antibodies by gender (years 2004-2005).*

	Anti-toxoplasma antibodies			
Elisa	*Men*	*Women*	*P*	*Total patients*
IgG positive	227 (42.27%) 95% CI: 38.09-46.45	348 (42.28%) 95% CI: 38.90-45.66	NS*	575 (42.28%) 95% CI: 39.65-44.91
IgM positive	19 (3.54%) 95% CI: 1.98-5.10	36 (4.37%) 95% CI: 2.97-5.77	NS*	55 (4.04%) 95% CI: 2.99-5.09
TOTAL	537	823		1360

*Not significant

TABLE 3 - *ELFA positivity for IgM anti-Toxoplasma antibodies among the ELISA-positive samples of patients and pregnant women (years 2004-2005).*

	Elfa positivity for anti-toxoplasma IgM			
	Group A (highly IgM positive at ELISA)	*Group B (weakly IgM positive at ELISA)*	*P*	*Total*
Patients	30/31 96.77% 95% CI: 90.55-100	14/24 58.33% 95% CI: 38.61-78.05	<0.01	44/55 80.00% 95% CI: 69.43-90.57
Pregnant women	16/16 100% 95% CI: 82.93-100	15/26 57.69% 95% CI: 38.70-76.68	<0.01	31/42 73.81% 95% CI: 60.51-87.11
Total	46/47 97.87% 95% CI: 93.74-100	29/50 58.00% 95% CI: 44.32-71.68	<0.01	75/97 77.32% 95% CI: 68.99-85.65

ing the follow-up. The three subjects who could not be followed up were negative for IgM at ELFA.

In the case of eight subjects who were weakly IgM positive at ELISA and IgG positive, and showed a high degree of IgG avidity, we had files documenting the presence of IgM 2-7 years before. As subjects with borderline or low avidity have recently been infected, the positive predictive value of the IgM screening test was 60.00% for the patients and 27.03% for pregnant women (Table 5). These values increased to 83.87% in the patients who were highly IgM positive at ELISA, and to 50.00% in pregnant women (Table 5). In the case of the subjects who were weakly IgM positive at ELISA, they went down to 21.05% among patients and 9.52% among pregnant women (Table 5).

TABLE 4 - *High, low or borderline avidity in samples patients and pregnant women positive for IgM anti-Toxoplasma antibodies at ELISA (years 2004-2005).*

		Anti-Toxoplasma IgG avidity			
		Group A (highly IgM positive at ELISA)	*Group B (weakly IgM positive at ELISA)*	*P*	*Total*
Patients	High avidity	5/31 16.13%	15/19 78.95%	<0.01	20/50 40.00%
	Low or borderline avidity	26/31 83.87%	4/19 21.05%		30/50 60.00%
Pregnant women	High avidity	8/16 50.00%	19/21 90.48%	<0.01	27/37 72.97%
	Low or borderline avidity	8/16 50.00%	2/21 9.52%		10/37 27.03%
Total	High avidity	13/47 27.66%	34/40 85.00%	<0.01	47/87 54.02%
	Low or borderline avidity	34/47 72.34%	6/40 15.00%		40/87 45.98%

TABLE 5 - *Positive predictive value of IgM anti-Toxoplasma antibody ELISA in patients and pregnant women (years 2004-2005).*

	Positive predictive value		
	Group A (highly IgM positive at ELISA)	*Group B (weakly IgM positive at ELISA)*	*Total*
Patients	83.87% 95% CI: 70.92-96.82	21.05% 95% CI: 2.72-39.38	60.00% 95% CI: 46.42-73.58
Pregnant women	50.00% 95% CI: 25.50-74.50	9.52% 95% CI: 0.00-22.07	27.03% 95% CI: 12.72-41.34
Total	72.34% 95% CI: 59.55-85.13	15.00% 95% CI: 3.93-26.07	45.98% 95% CI: 35.51-56.45

DISCUSSION

The severity of congenital *Toxoplasma gondii* infection means that a precise diagnosis of acute infection during pregnancy is very important and, as it is often asymptomatic, this can only be done by means of laboratory tests. The search for IgM has been widely used for this purpose, but the correct interpretation of positive cases is essential because the possible aspecificity and extended permanence of the IgM, which can give rise to misinterpretations suggesting the need to interrupt a pregnancy or start a treatment that may be useless or even harmful because of its possible teratogenic effects (Gras *et al*., 2001). In addition to this, it is of course also necessary to consider maternal anxiety over the evolution of the pregnancy and the related psychological problems. It is therefore important to define the real probability that a positive IgM test actually indicates the presence of acute infection: i.e. its real positive predictive value. The published data are disappointing insofar as they indicate the positive predictive value of commercial IgM tests is only 6%.

Predictive value depends on the prevalence of the infection in a given population. Our case records indicate a global prevalence of anti-*Toxoplasma* IgG antibodies (which is thought to reflect actual exposure) is 27.41% (95% CI: 26.15-28.67), with a difference between patients undergoing clinical check-ups (42.28%; 95% CI: 39.65-44.91) and pregnant women undergoing serological screening (21.51%; 95% CI: 20.13-22.89), although it must be remembered that the age ranges of these two groups is very different (from one month to 91 years *versus* 15-44 years), and that the patient group included some undergoing a general check-up and others being investigated because of a precise diagnostic suspicion.

The global prevalence of IgM, an index of possible recent infection, was 2.03% (95% CI: 1.63-2.43): 4.04% (95% CI: 2.99-5.09) among the patients and 1.23% (95% CI: 0.86-1.60) among the pregnant women.

Given the well-known limitations of IgM tests, the results of the ELISA screening test were verified using the IgM ELFA test. Globally, 77.32% were confirmed without any differences between the patients and pregnant women. However, regardless of the test used, IgM can persist long after the infection and, as previously described in the literature, we had cases in whom IgM was present 2-7 years before, thus confirming that testing IgG avidity is indispensable for characterising the infection.

Only 45.98% (95% CI: 35.51-56.45) of our subjects who were IgM positive at the screening test showed low or borderline avidity, an index of a recent infection probably occurring in the four months preceding blood sampling (Holliman *et al*., 1996). Assuming that these subjects had truly been recently infected, this represents the positive predictive value of the IgM ELISA test. However, the predictive value changes considerably depending on the level of IgM positivity and the group being studied. Among our patients, the positive predictive value increased to 83.87% (95% CI: 70.92-96.82) in those who were highly IgM positive at ELISA, but went down to 21.05%

(95% CI: 2.72-39.38) in those who were weakly positive; and the corresponding figures among the pregnant women were 50.00% (95% CI: 25.50-74.50) and 9.52% (95% CI: 0.00-22.07). In asymptomatic patients (such as a pregnant woman may be) only one in two cases that are highly IgM positive corresponds to a recent infection, against one in ten cases that are weakly positive.

Our records show that the presence of weak IgM positivity and high IgG avidity may be due to a past infection occurring as many as seven years previously, whereas the presence of weak IgM positivity without IgG may not only indicate a more recent infection, but also be aspecific. In our patients who were followed up, it was possible to document both the continuing presence of weak IgM positivity and its disappearance in the absence of IgG.

In conclusion, our data indicate that a finding of high IgM positivity in subjects undergoing a clinical check-up indicates a recent infection in approximately 80% of cases, but the low predictive value in pregnant women makes it necessary to undertake additional tests. Even more clearly, the result must be doubted in the case of weak IgM positivity and in the absence of IgG. If it is not possible to perform an avidity test, it is essential to arrange for follow-up serological examinations during pregnancy.

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