Evaluation of the Second Generation IMx Toxo IgG Antibody Assay for Detection of Antibodies to *Toxoplasma gondii* in Human Sera

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For an evaluation of the Abbott IMx Toxo IgG second generation, antibodies to *Toxoplasma gondii* were detected by Abbott IMx Toxo IgG and IgM, Vidas Toxo IgG and Toxo IgM (bioMérieux, France) with immunofluorescence assay verified by the dye-test for IgG, and immunosorbent agglutination assay (ISAGA) for IgM as references. The study included 507 serum samples collected over one month in two laboratories, 32 samples from HIV-infected patients, and 70 serial samples from 23 women surveyed for seroconversion or persistent IgM. After exclusion of nine equivocal results from the 507 samples, the sensitivity and specificity, re-

spectively, were 100% (156/156) and 100% (342/342) for the IMx Toxo IgG and 98.1% (153/156) and 100% (342/342) for the Vidas Toxo IgG. Of the 32 HIV-infected patient samples, 7 gave false positive results with IMx Toxo IgG. This was because the samples had been heated. In 5 of the 70 serial samples, IMx Toxo IgG gave positive results earlier than Vidas Toxo IgG and in two cases earlier than IgM antibody assays.

In this study IMx Toxo IgG second generation showed an increase in sensitivity and specificity in comparison with data reported previously for the first generation. J. Clin. Lab. Anal. 11:214–219, 1997. © 1997 Wiley-Liss, Inc.

Key words: acquired, congenital, and AIDS-related toxoplasmosis; serodiagnosis; immunoenzyme techniques

INTRODUCTION

Toxoplasmosis is common in France. It can cause embryopathy, fetopathy, and ocular toxoplasmosis in pregnant women (1–3). It can also produce serious effects in AIDS patients and organ recipients. The serological status of these high-risk subjects is therefore routinely surveyed. It is important to initiate early treatment in expectant mothers, to reduce congenital infection and to avoid neurological deterioration in newborns and infants (2,4), and in AIDS patients, to reduce the severity of encephalitis (5). Tests of high specificity are hence required to avoid wrongly eliminating a pregnant woman from survey, or starting a treatment because of false positive reactions.

The second version of a commercial assay, IMx Toxo IgG (Abbott Diagnosis, Rungis, France), was recently developed, using a microparticle enzyme immunoassay (MEIA). The aim of this study was to evaluate the sensitivity and the specificity of this assay in comparison to those used as references in our laboratory on sera of patients of unknown serological status, and to observe the performances of the test in identified seroconversions and in HIV-infected patients.

MATERIALS AND METHODS

Serum Samples

All the 539 serum samples collected during the month of June 1995 in the laboratories of the hospitals of Grenoble and Clermont-Ferrand were tested. They were from patients with a mean age of 30 years (range 0–89): 97 were male and of the 442 female, 372 were pregnant. The results of the 32 serum samples from 29 HIV and 3 AIDS patients were analyzed separately. These patients (9 females and 23 males) had a mean age of 37 years (range 25–57). They did not develop toxoplasmic encephalitis. Thirty of the 32 serum samples were heated at 57°C, since the HIV status was known before assay. In addition, 56 serum samples from 19 pregnant women who had seroconverted during pregnancy and 14 serum samples from 4 adults with persistent IgM were included.

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MEIA

The IMx Toxo IgG second generation (Abbott Division Diagnostic F94518 Rungis) was used for IgG antibody detection. The microparticles, which are coated with *Toxoplasma gondii* antigen, are incubated with the patient specimen. *T. gondii*-specific antibodies react with the antigen-coated microparticles and an aliquot of the antigen-antibody complex is transferred to a glass fiber, which captures the microparticles. The matrix is washed off the unbound components. A goat antihuman IgG antibody conjugated to alkaline phosphatase, and the enzyme substrate, methylumbelliferyl phosphate, are used to detect the presence of IgG antibody bound to the *T. gondii* antigen on the solid phase. The rate of fluorescence developed by dephosphorylated methylumbelliferone is measured by the front surface fluorometer within the IMx analyzer. The results are quantitative and are converted to International Units per millimeter (IU/ml) from a calibrated curve generated with calibrators matched to the World Health Organization International Standard for Anti-Toxo Serum. The results were interpreted as follows: 0.000–1.999, negative; 2.000–2.949, equivocal; 2.950 or greater, positive.

IMx Toxo IgG was used for IgM antibody detection. The procedure is the same as for IgG antibodies except that a goat antihuman IgM antibody is used. The results are qualitative and are expressed as an index derived by dividing the patient specimen value by the value of the index calibrator included in each run. Index results were interpreted as follows: 0.000–0.499, negative; 0.500–0.599, equivocal; 0.600 or greater positive. The samples with an index greater than 0.499 were treated with the MEIA rheumatoid factor neutralization reagent.

VIDAS (bioMérieux F69280 Marcy L'Etoile)

VIDAS TXG uses an automated enzyme-linked fluorescent immunoassay which enables IgG *Toxoplasma* antibodies to be quantitatively measured. Solid-phase receptacles coated with membrane and cytoplasmic *Toxoplasma* antigen constitute a disposable pipette-like tip device. Reagents are contained in a foil-sealed 10-well reagent strip. The first well is for the sample and the following wells contain washing buffers, mouse monoclonal antihuman IgG antibodies conjugated to alkaline phosphatase, and methylumbelliferyl phosphate. The results are expressed in IU/ml in relation to a calibration curve stored in the VIDAS memory. Every 14 days the system is calibrated by calibrators matched to the World Health Organization International Standard for Anti-Toxo Serum. The assay was performed according to the manufacturer's directions. The results were interpreted as follows: <8 IU/ml, negative; from 8 to 10 IU/ml, equivocal; ≥ 10 IU/ml, positive.

VIDAS TXM uses the same automated method as VIDAS TXG. The solid-phase receptacles are coated with goat anti-

human μ chain antibodies and the strips contain an alkaline phosphatase-labelled immune complex made up of a *Toxoplasma* antigen linked to mouse monoclonal anti-P30 antibodies. Final results are expressed as a test value, which is the ratio of relative sample fluorescence to that of the standard. Interpretation was based on the following thresholds: <0.55 absence of IgM antibodies; between 0.55 and 0.65 equivocal result; ≥ 0.65 presence of IgM antibodies.

Indirect Immunofluorescence Assay (IFA)

The antigen is obtained from tachyzoites of the RH strain. Anti-toxoplasma IgG are detected by fluorescein-labelled antihuman IgG antibodies. The threshold for positivity is 8 IU/ml, which corresponds to a serum dilution of 1/20 (6).

The positivity threshold for the IgM is titer 1/40. Adsorption of IgG is used when their titer is >1/320 to avoid false negative IgM detection. Adsorption of rheumatoid factor is used when IgM detection is positive to avoid false positive IgM detection.

Immunosorbent Agglutination Assay (ISAGA) (bioMérieux F69280 Marcy L'Etoile)

Ninety-six well plates coated with antihuman IgM monoclonal antibodies are incubated with patients' serum (7). Specific IgM *Toxoplasma* antibodies are revealed by the addition of formalin-treated *Toxoplasma* organisms. If the reaction is negative, sedimentation of the *Toxoplasma* occurs in a smooth button. If the reaction is positive, the *Toxoplasma* are agglutinated in a mat and any antigen in excess of the bound specific IgM forms an equivalent amount of sediment. This allows a reading of values ranging from 0 to 12 because the sera are tested with three concentrations of antigen. Values of 5 or lower are interpreted as negative, between 6 and 8 equivocal, and 9 or greater as positive.

Dye-Test and High-Sensitivity Direct Agglutination (HSDA)

Both assays were performed by Docteur Ph. Thulliez (Institut de Puériculture, Paris, France) when the result of IgG detection with one test was at variance with that of the other tests (8–10). The positivity threshold was 2 IU/ml for the dye-test and 4 IU/ml for HSDA.

Technical Performance Comparison

Sera with equivocal results were retested with the method that gave equivocal results. The second value was taken as the final result. Nine sera for which the retest value remained equivocal in one of the assays were excluded from analysis. Agreement between two methods was defined as the percentage of specimens that gave the same results, positive or negative, in both. Sensitivity and specificity were calculated with IFA as reference for IgG.

RESULTS

Tables 1 and 2 show the distribution of the results obtained on the 498 serum samples after the exclusion of nine equivocal results.

In the detection of IgG *Toxoplasma* antibodies, IFA IgG gave 154 (30.9%) positive and 344 (69.1%) negative results. With IMx Toxo IgG, 156 were positive and 342 negative (Table 1). Using IFA as reference, we obtained two false positive results which were confirmed positive by the dye-test (sera 1 and 2, Table 3). Thus, the sensitivity and specificity of IMx Toxo IgG was 100% (Table 2) and the agreement between IMx and IFA was 99.6% (496/498). Of the 15 sera with equivocal results in the first run in IMx Toxo IgG, 4 gave repeated equivocal results and were excluded from the analysis. In Vidas TXG, 153 serum samples were positive and 345 negative (Table 1). After the dye-test, three samples gave false negative results with values ≥ 5 IU/ml in Vidas TXG (sera 1–3, Table 3). Five equivocal results were found in the first run and one in the second. Sensitivity was 98.1% (153/156) and specificity 100% (342/342) (Table 2) and agreement 99.8% (497/498) with IFA and 99.4% (495/498) with IMx.

In the detection of IgM *Toxoplasma* antibodies with ISAGA, 15 (3.0%) serum samples were positive and 483 (97.0%) were negative and 1 was equivocal. With IMx Toxo IgM, 14 were positive, 484 were negative, and 3 were equivocal, including one serum sample giving an equivocal result in ISAGA. The false negative result index was 0.468, close to the threshold (sera 4 and 5, Table 3). The agreement with ISAGA was 99.8% (497/498). With Vidas TXM, 13 positive and 485 negative results were obtained and 1 equivocal at the first and second runs. There were two false negatives. The agreement with ISAGA was 99.6% (496/498) and with IMx 99.8% (497/498). In IFA, four samples were positive and 494 were negative for the IgM.

Of the 32 samples of HIV-infected patients (Table 4), 22 were positive and 10 were negative with IFA for the IgG. In IMx Toxo IgG, only two samples were negative. Thus, in comparison to IFA, IMx Toxo IgG gave eight false positive results (sera 6–13, Table 3), of which seven were confirmed negative by the dye-test (sera 7–13, Table 3). With Vidas TXG, 22 samples were positive and 10 negative. IgM *Toxoplasma* antibodies were not detected in these samples and all the assays were in agreement.

TABLE 1. Results of the 498 Routinely Collected Serum Samples After Exclusion of Equivocal Results

Interpretation according to the test	IgG			
	IFA	IFA + Dye-test ^a	IMx	Vidas
Positive	154	156	156	153
Negative	344	342	342	345
Total	498	498	498	498

^aIFA was used as a reference test and the dye-test for the resolution of discrepancies.

TABLE 2. Sensitivity and Specificity of IMx and Vidas on 498 Serum Samples^a

	IgG ^b	
	IMx%	Vidas%
Sensitivity (%)	100 (100)	99.4 (98.1)
Specificity (%)	99.4 (100)	100 (100)

^aValues in parentheses were obtained after testing the sera, which gave discordant results with the dye-test.

^bIFA was used as reference.

In 7 of the 19 women who had seroconverted, the kinetics of tests were all in agreement. In three cases, IMx Toxo IgG gave positive results before IFA IgG (1b, 2a, and 3a, Table 5) and in two cases equivocal results when the other methods were negative (4a and 5a). In cases 2 and 6, IMx Toxo IgG gave positive results before the assays which detected IgM *Toxoplasma* antibodies.

In Vidas TXG, seven negative (1c, 3a and b, 7b, and 8a–c) and two equivocal samples (6a and 9b) were at variance with IFA IgG and/or IMx but, except in 6a, Vidas TXM gave positive results. In cases 10b and 11c, ISAGA was equivocal and the results were positive in IMx Toxo IgG and Vidas TXM. For sample 1b, IMx Toxo IgG gave positive results before Vidas TXM and ISAGA, whose results were equivocal. In case 12, the results in the IMx Toxo IgM and Vidas TXM became negative before ISAGA (12d). There was no discrepancy in results of the four patients with persistent IgM, between ISAGA, IMx Toxo IgG, and Vidas TXM.

DISCUSSION

IMx and Vidas are two of the most widely used methods for the detection of anti-*Toxoplasma* antibodies in French laboratories. There have been very few reports in which IMx first or second generation was used (11,12). The method adopted in our study differs in several respects from those described elsewhere (5,13–19).

The 508 serum samples were collected over one month without selection in two hospitals 300 km apart (18,19) and not on the basis of the results obtained with another assay (13) or according to clinical status (5,14–17). All the tests were performed in the same laboratory, which avoids variations linked to center (20). The results of IgM *Toxoplasma* antibody detection are given here because detection is routinely combined with IgG *Toxoplasma* antibodies in France. They are useful in determining serological status and in differentiating recent and former seroconversions to *Toxoplasma* (21), especially in cases of discordant results in IgG titers between two tests and in the serial samples of seroconverted women.

Both Abbott-IMx and Vidas were easy to use. Vidas has the advantage of being able to test IgG and IgM in the same run when there are fewer than 24 sera. The results of the detection of the IgG of the 507 samples showed an excellent

TABLE 3. Discordant Results Between the Different Tests^a

Sample	IgG (IU/ml)					IgM				
	IFA	Dye-test	HSDA	IMx	Vidas	ISAGA index	IMx index	Vidas ratio	IFA titer	Clinical status
1	0	4	4	3.0	5	0	0.433	0.00	0	p
2	0	2	16	3.3	5	0	0.307	0.09	0	CT
3	8	5	16	3.1	7	1	0.280	0.11	0	CT
4	80	ND	ND	48.2	80	12	0.468	0.38	0	P
5	80	ND	ND	27.9	79	12	0.710	0.16	0	P
6	0	4	8	3.0	7	1	0.280	0.11	0	HIV
7	0	<1	2	4.5	1	0	0.263	0.05	0	HIV
8	0	<1	0.4	7.0	5	0	0.456	0.02	0	HIV
9	0	<1	0.4	3.8	3	0	0.334	0.16	0	HIV
10	0	<1	0.2	4.0	2	0	0.335	0.05	0	HIV
11	0	<1	0.2	3.4	1	0	0.280	0.00	0	HIV
12	0	<1	<0.2	7.9	1	0	0.426	0.02	0	HIV
13	0	<1	1	4.1	3	0	0.189	0.02	0	HIV

^aP, pregnant women; CT, corneal transplantation; HIV, HIV-infected patient. Threshold IgG positive: IFA ≥ 8 , dye-test ≥ 2 , HSDA ≥ 4 , IMx ≥ 2.95 , Vidas ≥ 10 . Threshold IgM positive: ISAGA ≥ 9 , IMx ≥ 0.6 , Vidas ≥ 0.65 , IFA $\geq 1/40$. Discordant results are given in bold face.

correlation between the different methods (99.4–99.8% agreement). The sensitivities and specificities of IgG detection were greater than those obtained with the first generation by Schaefer et al. (11) (respectively, 98.0% and 97.5%) and those given by the manufacturer. In IMx Toxo IgG, the manufacturer, using another commercial EIA assay as reference, reported 99.6% sensitivity and 99.4% specificity. Taking Vidas TXG as reference, we obtained 100% sensitivity and 99.1% specificity in IMx Toxo IgG, which are very close to the respective values of 99.9% and 99.1% reported by Bevirt et al. (22) with the same assays. This underlines the importance of using standard tests as reference in evaluating new assays and in comparing the results of different reports.

With Vidas TXG, specificity was greater after the dye-test but sensitivity was lower in our study than those of the manufacturer with a different EIA assay as reference in combination with the dye-test (sensitivity 98.4%, specificity 99.7%). In a previous study in the same laboratory, specificity was 99.4%, sensitivity 99.7%, and agreement 99.5% (18). It is noteworthy that the values (of 5 and 7 IU/ml) obtained for the three samples which gave false negative results with the Vidas TXG were greater than zero (Table 3, sera 1–3).

There were few positive sera for the detection of IgM *Toxoplasma* antibodies because some were included in the survey of women who had seroconverted or who had persistent IgM.

TABLE 4. Results Obtained for the 32 Serum Samples From HIV Patients

No. of sera	IgG <i>Toxoplasma</i> antibody assay			
	IFA	IFA + dye-test ^a	IMx	Vidas
Positive	22	23	30	22
Negative	10	9	2	10

^aIFA was used as a reference test and the dye-test was used for the resolution of discrepancies.

It has been reported that HIV seroconversion does not influence the seroprevalence of toxoplasmosis (5,23). The higher proportion of sera positive for IgG *Toxoplasma* antibodies in HIV patients in our study than in the other routinely collected sera could therefore be explained by the regular survey of pregnant women, who are seronegative for *Toxoplasma* and thereby increase the proportion of negative samples. The false positivity of seven results was probably due to the laboratory policy of heating the HIV samples, and confirms the manufacturer's recommendation not to use IMx for heated samples. Similar discrepant results with heated sera were reported, to a lesser degree, by Luyasu et al. (20) with IMx Toxo IgG when testing 546 sera from the United States, but not with European sera. In the USA sera, HIV-infected patient sera were included. The authors observed that indexes of negative sera were lower in nonheated sera than in heated specimens. It is noteworthy that of the two nonheated samples one was sample 6, for which the result was positive with IMx Toxo IgG and confirmed by the dye-test, and for which the result was negative with Vidas TXG.

The difficulties reported in the different studies on samples from HIV-positive patients lie more in the detection of the beginning of acute toxoplasmosis episodes than in the detection of IgG anti-*Toxoplasma* in HIV-positive patients (2,16). A serological survey of a cohort of HIV patients, without the use of heated sera, would be necessary to evaluate the sensitivity of IMx in such cases.

There are few published reports in which sequential samples from the same patient were used for the diagnosis of maternal *Toxoplasma* infection because, except in France and Austria, systematic and repeated surveys of the serological status of pregnant women are only rarely performed. Estimating at what point during pregnancy the patient first comes into contact with the infection is made easier by the use of several tests with different kinetics, especially if the number of

TABLE 5. Discrepant Results in *Toxoplasma* Serology in Women Who Seroconverted During Pregnancy^a

Patient	Sample	Time ^b (week)	IgG (IU/ml)			IgM			
			VIDAS	IFA	IMx	VIDAS ratio	ISAGA index	IF titer	IMx index
1	a	0	1	0	0.6	0.00	0	0	0.207
1	b	5	0	0	8.5	0.59	6	0	2.520
1	c	7	2	80	14.9	4.73	11	160	1.007
2	a	0	0	0	4.6	0.07	0	0	0.398
2	b	4	11	8	15.8	1.84	9	40	1.993
3	a	0	3	0	7.5	2.99	12	80	1.740
3	b	1	5	8	8.7	3.04	12	80	1.670
4	a	0	0	0	2.0	0.13	6	0	0.421
4	b	2	198	320	300.0	0.65	9	0	0.757
5	a	0	0	0	2.2	0.04	0	0	0.238
5	b	8	10	8	120.2	4.73	12	160	5.160
5	c	9	32	80	120.2	5.64	12	160	5.712
6	a	0	9	8	3.8	0.22	3	0	0.388
6	b	10	18	80	19.6	3.57	12	160	3.419
6	c	46	300	640	300.0	1.19	9	0	0.745
7	a	0	0	0	1.2	0.00	0	0	0.245
7	b	32	6	8	20.4	2.47	11	40	1.789
7	c	34	43	160	118.2	2.33	11	40	1.692
8	a	0	0	8	3.5	4.86	12	40	2.263
8	b	1	1	8	3.8	4.90	11	80	1.940
8	c	12	3	8	6.6	2.80	11	80	2.157
9	a	0	0	0	0.7	0.00	0	0	0.227
9	b	4	9	8	29.5	3.73	12	40	4.956
10	a	0	0	0	0.3	0.11	0	0	QI
10	b	8	127	320	300.0	1.29	6	0	0.872
11	a	0	0	0	0.8	0.07	0	0	0.234
11	b	4	0	0	0.4	0.07	0	0	0.221
11	c	20	33	8	43.0	0.85	8	40	0.882
11	d	21	31	80	37.5	0.76	10	40	0.491
12	a	0	40	160	80.8	1.57	12	80	1.278
12	b	2	85	320	233.5	1.14	12	80	1.011
12	c	6	160	1280	300.0	0.64	9	40	0.552
12	d	10	150	1280	300.0	0.53	9	40	0.436
12	e	12	132	640	284.4	0.51	6	0	0.456

^aThreshold IgG positive: IFA ≥ 8 , dye-test ≥ 2 , HSDA ≥ 4 , IMx ≥ 2.95 , Vidas ≥ 10 . Threshold IgM positive: ISAGA ≥ 9 , IMX ≥ 0.6 , Vidas ≥ 0.65 , IFA $\geq 1/40$. In seven other women, the kinetics of tests were all in agreement.

^bThe first sample was arbitrarily dated 0 weeks and the time in weeks thereafter was calculated for the following samples in the same patient. Discrepant results are given in bold face.

samples for the same patient is low. The discrepancies between the kinetics of the tests were sometimes of no consequence. In patients 4 and 5, there were equivocal or negative results and so a second sample was taken, which showed seroconversion. In patients 3, 7, 8, and 9, Vidas gave negative results for IgG only and the diagnosis of seroconversion was made on the basis of IgM detection, which was positive whatever the test used. But in patients 1, 2, and 6, IgG *Toxoplasma* antibodies were detected earlier with IMx Toxo IgG than with Vidas TXG. IMx could be used to estimate the time of seroconversion, but if it is used alone there is the risk that patients such as 2 and 6 would be considered as being already seropositive because the IgG antibodies were positive before the IgM antibodies.

In countries where the prevalence of *Toxoplasma* infection is very low, it would be possible to detect seroconversion in a highly sensitive assay for IgG *Toxoplasma* antibody detec-

tion and to confirm positivity by a second sample a few days later using the combination of IgG and IgM detection (24). Such a policy would be cheaper than the survey of seronegative patients and acceptable because, if hygiene rules are respected, the risk of primary infection is low. Conversely, in countries with a high prevalence of toxoplasmosis, the screening of seroconversion among patients seropositive for *Toxoplasma* should be done with the first sample. It would be more expensive to detect seroconversion by a second assay in seropositive patients and as the risk of seronegative pregnant women acquiring toxoplasmosis is higher than in other countries, a serological survey would be justified. Thus, the sensitivity of IgM detection must be as great as that of IgG detection in order to maintain the ability to distinguish between those with recently acquired infection and subjects with long-standing immunity (25).

In France, in addition to nutritional and hygiene measures,

the prevention of congenital toxoplasmosis in pregnant women involves screening. This screening has two aims: the first is to detect seronegative subjects so as to begin monthly serological surveillance, and the second is the early detection of a seroconversion so as to initiate treatment and avoid congenital infection. Improvements to the test must take into account these two aspects of screening.

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