ORIGINAL INVESTIGATIONS

Assessment of antiphospholipid antibodies using enzyme-linked immunosorbent assay and chemiluminescent method

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AAntiphospholipid antibodies (aPL) are a sign of acquired thrombophilia and are associated with recurrent thrombosis and obstetric pathology. According 2006 classification criteria, serological markers of antiphospholipid syndrome (APS) include lupus anticoagulant, moderate and high levels of antibodies to cardiolipin (aCL) and β2-glycoprotein 1 (anti-β2-GP1) IgG and IgM. The task of standardizing aPL values remains unresolved, leading to variability in results.

***Objective:** to evaluate the comparability of IgG/IgM aCL and IgG/IgM anti-β2-GP1 measurement results using enzyme-linked immunosorbent assay (ELISA) and chemiluminescence (CLU) tests.*

***Material and methods.** Peripheral blood from 192 patients (147 women and 45 men) was analyzed, 55 patients (29%) had primary APS, 12 (6%) had probable APS, 61 (32%) had systemic lupus erythematosus (SLE) and APS, and 64 (33%) had SLE without APS. IgG/IgM aCL and IgG/IgM anti-β2-GP1 were determined in all participants by ELISA. By CLU method IgG/IgM aCL were analyzed in 192 patients and IgG/IgM anti-β2-GP1 in 191 patients.*

***Results and discussion.** The evaluation of the comparability of the results of ELISA and CLU revealed considerable discrepancies in the positive tests. Thus, in 16% of cases, a discrepancy was found in the levels of IgG aCL and IgM aCL by both methods (n=30 and n=31, respectively), in 18% in the level of IgG anti-β2-GP1 (n=34) and in 15% in the level of IgM anti-β2-GP1 (n=28). These discrepancies were to a greater extent associated with a more frequent detection of aPL in CLU when their values were negative in ELISA , indicating the greater information capacity of the CLU method.*

However, a small number of patients were positive for aPL in ELISA but negative in CLU: 5 with IgG aCL, 4 with IgM aCL, 6 with IgG anti-β2-GP1, and 2 with IgM anti-β2-GP1 .

***Conclusion.** CLU is shown to be a more informative method for determining IgG aCL and IgG anti-β2-GP1 than ELISA (p<0.05).*

***Keywords:** antiphospholipid antibodies; antiphospholipid syndrome; systemic lupus erythematosus; immunosorbent analysis; chemiluminated analysis; antibodies against β2-glycoprotein 1; antibodies against cardiolipin.*

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Introduction. The diagnosis of antiphospholipid syndrome (APS) is confirmed by the presence of antiphospholipid antibodies (aPL) in the blood, along with associated thrombosis or obstetric complications. Additionally, these antibodies play a key role in predicting the clinical manifestations of APS [1–4].

Current classification criteria for APS include only three types of aPL: lupus anticoagulant (LA), antibodies to cardiolipin (aCL), and antibodies to β2-glycoprotein 1 (anti-β2-GP1) of the IgG and IgM classes. The diagnosis of APS requires medium to high levels of these antibodies, confirmed in two consecutive measurements at least 12 weeks apart [5].

Traditionally, enzyme-linked immunosorbent assay (ELISA) has been used to detect aPL. However, this method is subject to interlaboratory variability and insufficient standardization, despite various recommendations [6]. Furthermore, ELISA may detect antibodies that lack pathogenic activity, reducing its specificity [7].

Newer methods, such as chemiluminescent assay (CLA), have been developed to improve diagnostic accuracy and standardize testing. This technique offers high analytical sensitivity and precision while minimizing interference from other substances [8].

The aim of this study was to compare the results of IgG/IgM aCL and IgG/IgM anti-β2-GP1 testing using enzyme immunoassay (ELISA) and chemiluminescent assay (CLA).

Material and Methods. The study included 192 patients (147 women and 45 men), of whom 55 (29 %) had primary APS (PAPS), 12 (6 %) had probable APS (proAPS), 61 (32 %) had SLE with APS, and 64 (33 %) had SLE without APS. Patient characteristics are presented in Table 1.

All patients were tested for IgG/IgM aCL, IgG/IgM anti-β2-GP1 by ELISA on an automatic analyser for laboratory diagnostics of autoimmune diseases Alegria (Orgentec Diagnostika GmbH, Germany) with a reagent kit for antibody determination by Orgentec Diagnostika GmbH (Germany). IgG aCL levels were measured in the phospholipid binding activity of IgG aCL at 1 μg/ml in GPL units (IgG phospholipid binding units (GPL U/ml), and IgM aCL levels were measured in the phospholipid binding activity of IgM aCL at 1 μg/ml in MPL (IgM phospholipid binding units (MPL U/ml). IgG/IgM anti-β2-GP1 levels were measured in U/ml. The positivity levels for IgG/IgM aCL and IgG/IgM anti-β2-GP1 are shown in Table 2.

IgG/IgM aCL in 192 patients and IgG/IgM anti-β2-GP1 in 191 patients were studied by the chemiluminescence method.

Table 1. Characteristics of patients

Parameter	Parameter value				
	PAPS (n=55)	proAPS (n=12)	SLE + APS (n=61)	SLE (n=64)	All (n=192)
Age , Me [25;75 percentile], years	38,0 [32,0; 43,0]	34,0 [29,5; 45,5]	40,0 [33,0; 46,0]	31,5 [24,0; 40,5]	37,0 [29,0; 43,5]
Duration of disease Me [25;75 percentile], years	8,9 [3,6; 13,0]	0,9 [0,3; 2,1]	12,0 [5,8; 19,0]	4,1 [1,8; 9,3]	7,0 [2,0; 15,0]
Gender: women/men, abs.	32/23	10/2	49/12	56/8	147/45
Thrombosis, n (%)	47 (90)	1 (8)	51 (86)	14 (22)	113 (60)
Venous thrombosis	21 (45)	0 (0)	24 (47)	10 (72)	55 (49)
Art. thrombosis	16 (34)	0 (0)	15 (29)	2 (14)	33 (29)
Art. and venous	10 (21)	1 (100)	12 (24)	2 (14)	25 (22)
Pregnancy failure, n (%)*	20 19 (95)	2 1 (50)	31 26 (84)	16 7 (44)	69 53 (77)
IgG aCL, n (%)	37 (71)	7 (58)	39 (66)	8 (12,5)	91 (49)
IgM aCL, n (%)	12 (23)	3 (25)	10 (17)	7 (11)	32 (17)
IgG+IgM aCL, n (%)	8 (15)	1 (8)	7 (12)	6 (9)	22 (12)
IgG anti-β_2-GP$_1$, n (%)	36 (69)	7 (58)	44 (75)	9 (14)	96 (51)
IgM anti-β_2-GP$_1$, n (%)	12 (23)	5 (42)	12 (20)	7 (11)	36 (19)
IgG+IgM anti-β_2-GP$_1$, n (%)	11 (21)	3 (25)	11 (19)	6 (9)	31 (17)

Note: values are presented as Me [25%; 75% quartiles] or number (percentage), n – number of patients in groups, arterial thrombosis, venous thrombosis; *obstetric pathology was calculated from the number of women who had a pregnancy on the background of the disease, in the numerator is the number of women who had a pregnancy on the background of the disease, in the denominator is the number of women with obstetric pathology.

Table 2. The limits of the degrees of positivity in the evaluation of the results of determination of aCL and anti-β_2-GP$_1$ [9]

Degree of positivity	aCL		anti-β_2-GP$_1$	
	IgG aCL, GPL	IgM aCL, MPL	IgG anti-β_2-GP$_1$, U/ml	IgM anti-β_2-GP$_1$, U/ml
Highly positive	≥65,0	≥45,0	≥60,0	≥60,0
Moderately positive	35,0–65,0	35,0–45,0	30,0–60,0	30,0–60,0
Low-positive	25,0–35,0	24,7–35,0	15,3–30,0	17,0–30,0
Negative	<25,0	<24,7	<15,3	<17,0

Note: aCL – antibodies to cardiolipin, anti-β_2-GP$_1$ – antibodies to β_2-glycoprotein 1.

CLA was performed on an automated chemiluminescent analyser BioFlash (Biokit S.A., Spain). The reagent kit for the determination of IgG/IgM anti-β_2-GP$_1$ and IgG/IgM aCL was AcuStar, Spain. All antibodies determined by CLA were measured in relative light units (RLU), with ≥20 RLU considered positive per the manufacturer's guidelines.

A control group of 100 relatively healthy individuals (86 women, 14 men) without rheumatic diseases, malignancies, or acute/chronic infections was included. Their mean age was 41.0 [30.0–54.0] years, comparable to the study group, with both groups being predominantly female. Based on the mean values of the control group for IgG/IgM/ aCL, IgG/IgM/ anti-β_2-GP$_1$, IgG/IgM/ anti-β_2-GP$_1$ positivity levels were allocated using the formulas: arithmetic mean (M) + 3 or 5 standard deviations (SD): M+3SD and M+5SD. The diagnostic value of the allocated positivity levels and the levels suggested by reagent manufacturers was assessed according to the formulas presented in Table 3.

The following positive levels were accepted according to the results of the analysis: for IgG aCL >25.9 CU (M+5SD), for IgM aCL >19.5 CU (M+3SD), for IgG anti-β_2-GP$_1$ >32.0 CU (M+5SD), for IgM anti-β_2-GP$_1$ >6.9 CU (M+3SD).

Statistical analysis of the results was performed using Statistica and Epi Info software. Descriptive statistics and non-parametric methods were applied. The statistical significance of the results was assessed using a false positive probability threshold of $p<0.05$. The mean (M) and standard deviation (SD) were used to describe central tendencies of quantitative traits with approximate normal distribution. For traits with non-normal distribution, the median (Me) and interquartile range, defined between the 25th and 75th percentiles, were given. The Mann-Whitney test was applied when comparing two independent groups for quantitative traits. The χ^2 test was used to analyse qualitative measures in two independent groups, with the Yates correction applied for 2×2 contiguity tables when the number of observations per cell was less than 5. If the number of observations was greater than 5, statistical processing of the data was performed in the Epi Info programme. In these cases, the standardised test was used to assess the statistical significance of χ^2, and the odds ratio with 95% confidence interval was calculated.

Table 3. Formulas for determining the metrics of the diagnostic value of the proposed positivity levels of the analyzed aPLs [10, 11]

Indicator	Formula
Sensitivity	True positives/true positives + false negatives
Specificity Specificity	True Negative/True Negative + False Positive
Accuracy (overall validity)	True positive + true negative/true positive + true negative/true positive + true negative + false positive + false negative
Likelihood ratio of a positive result	Sensitivity/1 – specificity
Likelihood ratio of a negative result	1 – sensitivity/specificity
Predictive value of a positive result	True positives/true positives + false positives
Predictive value of a negative result	True negatives/true negatives + false negatives
False positive rate	1 – specificity

The Cohen's Kappa value was used to measure the degree of consistency of the results of aPL determination by ELISA and CLA methods. The coefficient was calculated using the IBM SPSS 26.0 statistical software package. The Cohen's Kappa value was interpreted according to Table 4.

Results. In 96 (50%) of 192 patients, IgG aCL were positive by ELISA and in 118 (61%) by CLA. As shown in Table 5, IgG aCL were detected significantly more frequently in CLA (χ^2=5.11, p=0.02). The Kappa Cohen's coefficient was 0.667, indicating good agreement between the methods. In ELISA, 77 (80%) of 96 patients had highly positive IgG aCL levels, 17 (18%) had medium-positive levels, and 2 (2%) had low-positive levels. The median levels were: high-positive 120.0 [101.8–120.0] U/ml, medium-positive 49.1 [43.6–55.0] U/ml, and low-positive 28.2 [27.5-28.9] U/ml. In CLA, the median of highly positive IgG aCL levels was 632.6 [369.9–1714.0] CU. High-positive levels in CLA were significantly higher than medium-positive levels (p<0.0001), and medium- and low-positive levels did not differ.

compared to medium-positive levels in CLA and p<0.0001 compared to low-positive levels in CLA.

Thirty-one (16%) of 192 patients had discrepancies in IgG aCL levels between methods: 27 (87%) had negative results by ELISA and positive results by CLA, with a median of 41.0 [33.2–102.5] CU. The reverse discrepancies were observed in four patients.

IgM aCL were positive in 33 (17%) patients by ELISA and in 56 (29%) by CLA (Table 5). The detectability of IgM aCL was significantly higher in CLA (χ^2=7.7, p=0.005). The Kappa Cohen's coefficient was 0.537. In ELISA, 23 (70%) of 33 patients had high-positive levels, 2 (6%) had medium-positive levels, and 8 (24%) had low-positive levels. The median levels were: high-positive 69.9 [53.6–82.4] U/ml, medium-positive 39.2 [36.9–41.5] U/ml, and low-positive 27.5 [25.2–29.4] U/ml. The high-positive levels in the CLA study, which corresponded to the high-positive values in the ELISA, were significantly higher compared to the low-positive values in the CLA data (p=0.007); Table 5.

In 31 (16%) patients, there was a discrepancy in IgM aCL levels between methods. 27 (87%) of these were negative in ELISA and positive in CLA (median 31.1 [21.1–48.3] CU), and 4 (13%) were positive in ELISA and negative in CLA.

IgG anti-β_2-GP$_I$ were positive in 100 (52%) of 191 patients by ELISA and 122 (64%) by CLA (χ^2=9.83; p=0.001); Table 5. The Kappa Cohen's coefficient was 0.621. In ELISA, 66 (66%) of 100 had high-positive levels, 28 (28%) had medium-positive levels, and 6 (6%) had low-positive levels. Median: high-positive was 100.0 [86.6–100.0] U/ml, medium-positive was 46.7 [40.6–53.8] U/ml, and low-positive was 24.0 [21.1–24.8] U/ml. In CLA, the medians of high-, medium-, and low-positive levels were 3371.8 [1546.9–6100.0] CU, 1557.4 [1022.0–1976.9] CU, and 529.3 [420.4–705.9] CU, respectively. High-positive levels were significantly higher in CLA than low- and medium-positive levels (p<0.0001).

Of 191 patients, 34 (18%) had discrepancies in anti-β_2-GP$_I$ IgG levels between methods. 28 (82%) were negative by ELISA and positive by CLA (median 109.1 [67.5–313.5] CU). Six (18%) were positive by ELISA and negative by CLA.

Positive IgM anti-β_2-GP$_I$ levels were reported in 37 (19%) by ELISA and 61 (32%) by CLA (χ^2=7.91; p=0.004). The Kappa Cohen's coefficient was 0.615 (Table 5). In ELISA, 13 (35%) of 37 had high-positive levels, 11 (30%) had medium-positive levels, and 13 (35%) had low-positive levels. The median of high-positive levels was: 90.9 [84.7–100.0] U/ml. In CLA, the median values of high-positive levels were significantly higher than low- and medium-positive levels (p<0.0001 and p=0.009).

Twenty-eight (15%) patients had discrepancies in anti-β_2-GP$_I$ IgM levels between methods. 26 (93%) were negative by ELISA and positive by CLA, with a median of 15.3 [8.6–31.0] CU. Two (7%) had positive IgM anti-β_2-GP$_I$ by ELISA but negative by CHLA.

Figure shows the frequency of detection of IgG/IgM aCL and IgG/IgM anti-β_2-GP$_I$ by CLA and ELISA methods.

Discussion. Investigation of aPL is an integral part of the current classification criteria for APS [12]. In patients with suspected APS, identifying persistent circulating aPL is critical, as the clinical manifestations of APS are nonspecific and frequently complicated by various underlying conditions. Diagnostic tests for aPL must demonstrate both high sensitivity and specificity to

Table 4. Interpretation of the κ Cohen coefficient

κ Cohen value	Degree of coherence
<0,20	Very weak
0,21–0,40	Weak
0,41–0,60	Moderate
0,61–0,80	Good
0,81–1,00	Very good

Table 5. Comparison of the results of determination of aPL using ELISA and CLU

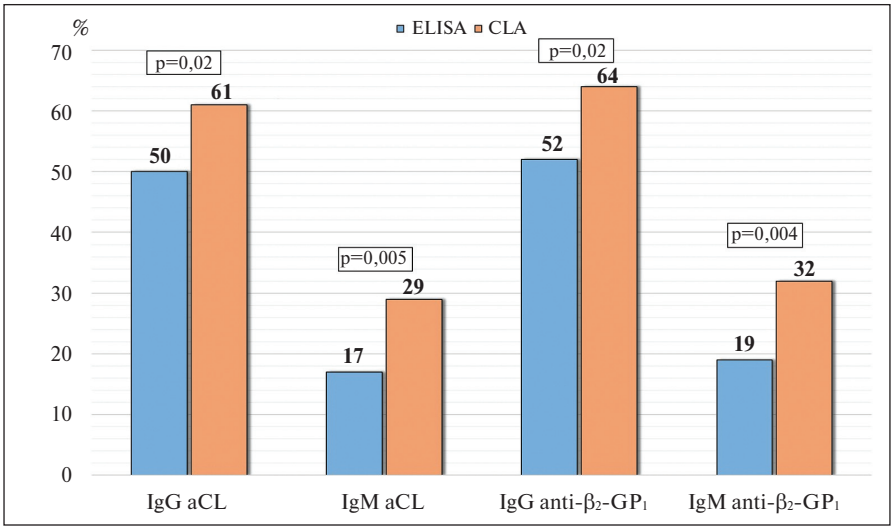
Indicator	ELISA			CLA		χ^2; p	κ; p
	Number of positive patients, n (%)		Levels of positivity in GPL/MPL, Me [25–75%]	Number of positive patients, n (%)	Levels of positivity in CU, Me [25–75%]		
IgG aCL, n=192	+	96 (50)	119,9 [69,6; 120,0]	118 (61)	406,2 [132,8; 981,1]	**5,11; 0,02**	0,667; 0,0001
	-	96 (50)		74 (39)			
Low-positive		2 (2)	28,2 [27,5; 28,9]		244,3 [8,3; 480,4]		
Medium-positive		17 (18)	49,1 [43,6; 55,0]	-/-	216,5 [105,0; 352,9]		
Highly positive		77 (80)	120,0 [101,8; 120,0]		632,6 [369,9; 1714,0]*		
IgM aCL (n=192)	+	33 (17)	55,2 [36,9; 80,0]	56 (29)	51,9 [29,6–142,0]	**7,74; 0,005**	0,537; 0,0001
	-	159 (83)		136 (71)			
Low-positive		8 (24)	27,5 [25,2; 29,4]		38,7 [24,5; 58,2]		
Medium-positive		2 (6)	39,2 [36,9; 41,5]	-/-	90,2 [82,5; 97,9]		
Highly positive		23 (70)	69,9 [53,6; 82,4]		155,0 [100,6; 122,8]**		
IgG anti-β2-GP1 (n=191)	+	100 (52)	86,6 [50,1; 100,0]	122 (64)	1810,5 [492,4; 4694,4]	**5,21; 0,02**	0,621; 0,0001
	-	91 (48)		69 (36)			
Low-positive		6 (6)	24,0 [21,1; 24,8]		529,3 [420,4; 705,9]		
Medium-positive		28 (28)	46,7 [40,6; 53,8]	-/-	1557,4 [1022,0; 1976,9]		
Highly positive		66 (66)	100,0 [86,6; 100,0]		3371,8 [1546,9; 6100,0]***		
IgM anti-β2-GP1 (n=191)	+	37 (19)	41,3 [25,0; 84,7]	61 (32)	35,4 [11,4; 117,6]	**7,91; 0,004**	0,615; 0,0001
	-	154 (81)		130 (68)			
Low-positive		13 (35)	19,0 [18,1; 25,0]		22,2 [13,6; 40,8]		
Medium-positive		11 (30)	41,3 [39,1; 51,7]	-/-	77,8 [11,4; 117,6]		
Highly positive		13 (35)	90,9 [84,7; 100,0]		187,2 [144,5; 258,2]****		

Note: n – number of patients, Me – median, [25%-75%] – interquartile range, p – frequency of occurrence comparison by contiguity table; «+» – positive, «-» – negative; -//- – the number of patients divided by the levels of positivity according to the CLA data correspond to the number of patients reported in ELISA; *p<0.0001 compared to medium-positive levels in CLA; **p=0.007 compared to low-positive levels in CLA; ***p=0.01 compared to medium-positive levels in CLA and p=0.002 compared to low-positive levels in CLA; ****p=0.009 compared to medium-positive levels in CLA and p<0.0001 compared to low-positive levels in CLA.

ensure accurate diagnosis, since misdiagnosis can significantly impact treatment strategies. Therefore, the choice and performance of assays to detect aPL should be carefully considered in accordance with international guidelines [13–16]. When considering aPL testing methods, it is important to emphasise that only patients with a high probability of developing APS should be screened for aPL [17]. Today, as aPL tests are ordered in a wider range of clinical disciplines, in real life there is a decrease in the percentage of probability of preliminary aPL positivity, and consequently a decrease in the probability of diagnosis after testing. This concern has been addressed in the recent American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria [12]. Routine aPL screening in asymptomatic individuals is generally discouraged to avoid detection of clinically irrelevant antibodies. Clinical scenarios warranting aPL testing include, for example, unexplained thrombosis in patients <50 years, thrombosis at atypical sites or with thrombotic complications, or pregnancy complications associated with concomitant autoimmune disease [12, 14]. Current guidelines recommend simultaneous testing of all aPL markers, with results interpreted in conjunction with clinical findings, given that aPL represent a heterogeneous group of autoantibodies with overlapping yet distinct characteristics.

The poor correlation between ELISA and non-ELISA aPL results is a serious problem [17]. Emerging methodologies like chemiluminescent assay (CLA) show promise for improving APS diagnosis [18–20]. Comparative studies demonstrate that CLA performs comparably or superiorly to ELISA for aPL detection [18,21–23]. For example, A. Capozzi et al [24] found that 30.13% of patients with negative LA and anti-β_2-GP1, but positive aPL by ELISA, had positive anti-β_2-GP1 values in CLA. In addition, 20% of patients with positive LA but persistently negative aCL and anti-β_2-GP1 values in ELISA had positivity in CLA data. According to our results, positive values of IgG/IgM aCL and IgG/IgM anti-β_2-GP1 were significantly more frequent in CLA study ($p<0.05$).

When assessing the comparability of ELISA and CLA, a large number of discrepancies in positive values were revealed. Thus, in 16% of cases there was a discrepancy in the levels of IgG aCL and IgM aCL according to both methods of deter-



Frequency of detection of IgG/IgM antibodies to cardiolipin and IgG/IgM antibodies to β2-glycoprotein 1 by chemiluminescent and enzyme immunoassays

mination (n=30 and n=31, respectively), in 18% in IgG anti-β_2-GP_1 (n=34), in 15% in IgM anti-β_2-GP_1 (n=28). To a greater extent, these discrepancies were associated with more frequent detection of aPL in CLA with their negative levels in ELISA, indicating more frequent detection of aPL by the CLA method.

However, a small number of patients were with positive aPL values in ELISA but negative in CLA: 5 with IgG aPL, 4 with IgM aPL, 6 with IgG anti-β_2-GP_1, and 2 with IgM anti-β_2-GP_1. Probably, the positivity of aPL according to ELISA data is due to the presence of low-affinity aPL that do not have pathogenic potential. It is known that for the manifestation of pathogenic properties of aPL, an aCL cofactor is required, which in most cases is identified as β_2-GP_1 [25]. Nonpathogenic aPL circulate in the blood and do not bind β_2-GP_1 and/or other cofactors [23].

Conclusion. In summary, our results on the comparability of two aPL assay methods (aCL and aβ_2-GP_1) showed that determination of aCL and aβ_2-GP_1 by CLA method is more informative than ELISA ($p<0.05$).

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