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Relevance of antiphospholipid antibodies in multiple sclerosis: A systematic review and meta analysis

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Background: The relationship between antiphospholipid antibodies (aPL) and multiple sclerosis (MS) is unclear.
Objectives: To evaluate a link between aPL and MS.
Methods: EMBASE and PubMed search to August 2016; Peto's odds ratio (OR) meta-analysis.
Results: The pooled prevalence of participants positive for IgG and IgM anticardiolipin (aCL) from 12 case–control studies was superior in MS than controls (6.8% vs 1.8%, $p = 0.01$ and 8.58% vs 2.18%, $p = 0.001$) with medium and high heterogeneities respectively ($I^2 = 48.55\%$ and 68.13%). The pooled prevalence of participants positive for IgG anti-beta$_2$glycoprotein-I (aβ_2GPI) from seven case–control studies was lower in MS than controls (0.93% vs 4.02%) with high heterogeneity ($I^2 = 53.92\%$) though the pooled prevalence of participants positive for IgM aβ_2GPI was similar (7.24% vs 6.13%) with high heterogeneity ($I^2 = 52.85\%$). Five cohorts compared IgG/IgM aCL and IgM aβ_2GPI in stable/remission vs active/relapsing MS: the pooled prevalence of IgG aCL was similar in active/relapsing and stable/remission MS (19% vs 18.9%) but the pooled prevalence of IgM aCL was higher in active than in stable MS (36.9% vs 21%, $p < 0.0001$) as well as that of IgM β_2GPI (40.5% vs 3.2%, $p < 0.0001$) with no heterogeneity.
Conclusion: Data from case–control studies do not support a link between IgG/IgM aPL and MS. Data from cohort studies comparing active vs stable MS indicate a strong link between aPL of IgM isotype and active/relapsing MS but in the absence of aPL titres to comment upon this may either represent an epiphenomenon of active neuro-inflammation or natural autoantibodies devoid of pathogenic potential. Data expressed as frequency of aPL positive participants rather than average titres preclude further assumptions.

Introduction

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system [1] and due to its autoimmune nature, markers of other autoimmune diseases have been evaluated in MS, particularly antiphospholipid antibodies (aPL), with a prevalence ranging from 2% to 88% [2]. Apart from recurrent vascular occlusions [3], the antiphospholipid syndrome (APS) is characterized by non-criteria manifestations affecting the central nervous system such as transverse myelitis and white matter lesions resembling MS (reviewed in two). However the MRI findings of MS suggest a greater degree T1- and T2-lesion volumes, lower brain parenchymal fraction, lower grey matter fraction, and higher mean parenchymal diffusibility than primary APS whereas the APS lesions seem more "vascular" than MS lesions [2]. On the other hand, MS patients with co-existent aPL could have an earlier age and more severe disease at presentation, worse vascular lesions and a more aggressive course. To appraise a link between aPL and MS we performed a systematic review and meta-analysis of available studies.

Methods

Search strategy and selection criteria

We carried out a systematic review according to the PRISMA guidelines [4]: PubMed and EMBASE databases were searched with the following terms: multiple sclerosis, anticardiolipin,

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antiphospholipid, anti-beta-2-glycoprotein-I, and lupus anticoagulant from January 1983 to August 2016. The reference list of retrieved papers was checked for references that could have been missed.

Criteria for selecting articles

Two investigators (M.M. and P.R.J.A.) independently assessed all retrieved studies. Inclusion criteria were as follows: (1) MS diagnosed according to established criteria; (2) observational study (case–control, cross-sectional, or cohort study) investigating the relationship between aPL and MS; (3) aPL measured via an accepted or described assay; (4) study reporting either the serum/CSF average titre of aPL or prevalence of participants positive for aPL; (5) if more than two studies investigated the same population, the latest or highest-quality study was chosen. Exclusion criteria were as follows: (1) the study was not original research; (2) prevalence studies only; (3) the study did not report the relationship between aPL and MS; (4) the study did not contain sufficient data to allow analysis; (5) articles not written in English, French, Spanish, Portuguese, or German. M.M. and P.R.J.A. screened all abstracts and applied the eligibility criteria to identify appropriate studies for inclusion and took into account date of publication, population, language, study design, participant data, and results.

Evaluation of the quality of the studies

The Newcastle Ottawa Quality Assessment Scale (NOQAS) assessed the quality of the case–control studies though they all compared two different groups with no real exposure to qualify as true case–control. The scoring system covers three major domains (selection of cases and controls, comparability of selected groups, and ascertainment of either the exposure or outcome of interest): the resulting score may range between 0 and 8, a higher score representing a better methodological quality. Data were independently extracted then inserted into an electronic spread sheet and any discrepancies were resolved by consensus.

Outcome measures and statistical analysis

The primary outcome measures are the pooled odds ratio (OR) and level of significance of the comparative pooled prevalence of participants positive for aPL in MS and controls groups (or between active/relapsing and stable/remission MS); the comparative pooled prevalence with level of significance is reported in the text whereas individual and pooled ORs are shown in the figures. The secondary outcome was the mean differences of aPL measured in serum and/or CSF in both MS patients and control groups where possible.

Statistical analysis was carried out using Comprehensive Meta-analysis Software Version 3 (Biostat, NJ, USA). As most of the collected data were expressed as proportion of participants positive for aPL in MS and controls we applied the Peto's method for pooled OR as it performs well in the presence of rare events [5]. For studies reporting continuous variables the meta-analysis investigated the average effect of the outcomes attributable to the MS group; that is a standardized mean difference between MS patients and controls. Because the estimates were the result of observational studies rather than planned experiments such as clinical trials we employed a random effect analyses in both instances.

Sensitivity analysis evaluated the robustness of the results of our meta-analysis: we excluded each study in turn and obtained the pooled estimates from the remaining studies: the results did not deviate from the overall pooled estimates. We employed empirical methods such as Funnel plots [6,7] in our preliminary investigations but the limited number of studies precluded formal tests for publication bias.

Statistical heterogeneity among studies was assessed by chi square Cochran's Q test and by I^2 statistics, which measures the inconsistency across study results and describes the proportion of total variation in study estimates due to heterogeneity rather than sampling error. An I^2 value of 0% indicates absence of heterogeneity, less than 25% indicate low, between 25% and 50% moderate and over 50% high heterogeneity. Subgroup analysis explored the source of heterogeneity between studies.

Results

After completion of the screening process (Fig. 1), 21 studies [8–29] met the criteria for inclusion in the analysis (Tables 1 and 2): of these, two [8,9] used the MS classification criteria of Rose et al. [30], seven [10,12,13,18,20,23,24] that of Poser et al. [31], one [11] that of Lee et al. [32], two [15,25] that of Polman et al. [33], two [22,28] that of Polman et al. [34] and three [16,17,29] that of McDonald et al. [35]; four studies did not report diagnostic criteria [19,21,26,27].

Quality of the studies

A score of ≥ 7 on the NOQAS was arbitrarily taken as a threshold for a good quality study: only three studies ranked seventh [10,24,29] (Tables 1 and 2). Reasons for achieving a low score were poorly documented inclusion/exclusion criteria for patients and control, failure to report age, sex, disease duration and/or disease activity, poor comparability. The agreement (Cohen's κ) of the 2 (M.A. and P.R.J.A.) NOQAS scorers was 0.566 (95% CI: 0.256–0.877).

Multiple sclerosis and serum IgG anticardiolipin antibodies

Twelve case–control studies on patients with different MS phenotypes explored the relationship between IgG aCL (anticardiolipin) antibody and MS [8–18,29]: a total of 992 MS patients and 944 healthy controls were available for the effect size of this outcome. The pooled prevalence of participants positive for IgG aCL was superior in MS than controls (6.8% vs 1.8%, $p = 0.01$) with moderate heterogeneity ($I^2 = 48.55\%$) (Fig. 2A).

Subgroup analysis

Subgroup analysis was performed on studies containing amongst cases a mixture of active and inactive MS phenotypes [6,7,13,15,27] and on those not reporting active and inactive phenotypes [10–14,16,18]. In the former case a total of 299 MS patients and 310 controls were available: the pooled prevalence of IgG aCL positive participants was greater in the MS than control group (11.7% vs 0.32%, OR = 5.958, 95% CI: 2.958–12.000, $p = 0.0001$) with no heterogeneity.

In the latter case 693 MS patients and 634 controls were available with a higher pooled prevalence of participants positive for IgG aCL in MS than controls (4.7% vs 2.5%, OR = 3.934, 95% CI: 0.977–15.848, $p = 0.05$) with high heterogeneity [($I^2 = 70.66\%$). Removal of one outlier study [11] changed the OR to 1.932; 95% CI: 0.717–5.207; $p = 0.19$] with 50% reduction in heterogeneity ($I^2 = 35.35\%$) suggesting that studies comprising a mixture of active and inactive MS phenotypes contribute to the heterogeneity of the overall analysis. Subgroup analysis by MS diagnostic criteria did not affect heterogeneity (data not shown).

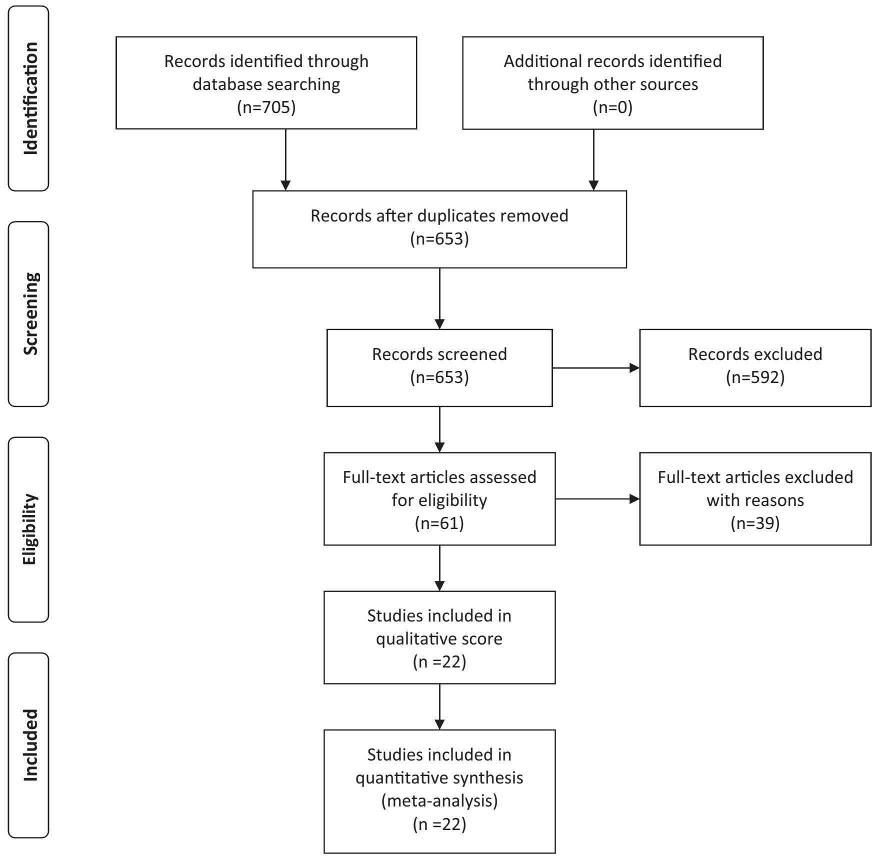

Fig. 1. Summary of literature search according to the PRISMA flow-chart. Full text excluded: $n = 14$: prevalence data only; $n = 9$: no data on antiphospholipid antibodies; $n = 5$: reviews; $n = 5$: data on optic neuritis only; $n = 3$: treatment related studies; $n = 3$: follow-up of multiple sclerosis with different outcomes.

Multiple sclerosis and serum IgM anticardiolipin antibodies

Eleven studies addressed the relationship between IgM aCL and MS [8–18]: a total of 885 MS patients and 869 controls were available for the effect size of this outcome: the pooled prevalence IgM aCL positive participants was higher in MS than controls (8.58% vs 2.18%, $p = 0.001$) with wide heterogeneity ($I^2 = 68.13\%$) (Fig. 2B).

Subgroup analysis

The analysis was re-run separately on those studies containing amongst cases a mixture of active and inactive MS phenotypes [8,9,15,17,29] and on those studies not containing active and inactive phenotypes [10–14,16,18]. In the former case a total of 172 MS patients and 218 controls were available: IgM aCL positive participants were over represented in the MS group compared to controls (19% vs 0.64%, OR = 7.660, 95% CI: 3.748–15.653, $p = 0.0001$) with moderate heterogeneity ($I^2 = 30.46$). In the latter case 586 MS patients and 559 controls were available with a pooled prevalence of IgM aCL positive participants similar in MS and controls (3.24 vs 3.04%, OR = 2.485, 95% CI: 0.634–9.744, $p = 0.019$) with wide heterogeneity ($I^2 = 58.78\%$). Removal of one outlier study (11) changed the OR (1.092, 95% CI: 0.498–2.397) with no heterogeneity. These split data suggest that studies comprising a mixture of active and inactive MS phenotypes cases contribute to the heterogeneity of the overall analysis. Subgroup analysis by MS diagnostic criteria did not affect heterogeneity (data not shown).

Multiple sclerosis and serum anticardiolipin antibodies with ischaemic stroke as disease control

Four studies addressed the relationship between IgG aCL and MS [8,20–22] using ischaemic stroke (IS) patients as disease controls: a total of 520 MS and 607 IS participants were available for the effect size of this outcome; the pooled prevalence of IgG aCL was lower in MS than IS (6.73% vs 8.4%, $p = 0.7$) with elevated heterogeneity ($I^2 = 74.44\%$) (Fig. 2C). Five studies addressed the relationship between IgM aCL and MS [8,19–22] totalling 537 MS and 617 IS patients: the pooled prevalence of IgM aCL was higher in MS than IS (9.40% vs 4.05%, $p = 0.3$) with elevated heterogeneity ($I^2 = 87.90\%$) (Fig. 2D).

Multiple sclerosis and mean serum IgG anticardiolipin antibodies

Five case–control studies reported mean serum levels of IgG aCL [20,23–25] but one did not mention the mean of the control group [20] and one reported the mean of positive MS patients only [29]: hence data from three case–control studies comprising 76 MS patients and 294 controls were pooled for the effect size of this outcome [23–25]. Random effect meta-analysis revealed wide heterogeneity amongst the studies ($I^2 = 95.7\%$, $p < 0.0001$) suggesting poor prospects for average pooled estimates (Fig. 2E).

Multiple sclerosis and cerebrospinal fluid anticardiolipin antibodies with systemic lupus erythematosus as disease control

Three studies addressed the relationship between aCL antibody and MS by measuring aCL in the cerebrospinal fluid of 110 MS patients and 28 systemic lupus erythematosus (SLE) patients

Table 1
Demographics of studies with multiple sclerosis as cases and normal subjects, ischemic stroke and systemic lupus as controls

				aCL		β_2GPI							aCL		β_2GPI		
	No	Age	M/F	IgG (%)	IgM (%)	IgG (%)	IgM (%)	No	Age	M/F	DD	A/R	IgG (%)	IgM (%)	IgG (%)	IgM (%)	NOS
	CTR							MS									
Chaleomchan et al[8]	111			18.75	0			16				16/0	0	0			**2**
Sugiyama and Yamamoto[9]	26	27–55	11/15	9.3	53.8			32	38 ± 21	13/19		16/16	9	0			3
Cordoliani et al[10]	31	37 ± 17	3/28	4.8	9.6	**3.2**	3.1	62	43 ± 23.6	25/37			3.2	1.6	4.8	4.8	7
Tourbah et al[11]	160	20–50	60/100	12	1.8			50	31 (15, 64)	57/104			0	0			6
Spadaro et al[12]	75	34 ± 7.5	26/49	16.1	22.6			105	37 ± 10.1	30/75	9.6 ± 7.8		2.6	1.9			5
Sastre-Garriga et al[14]	51	41 ± 11	32/19	0	0	**0**	0	251	38 ± 11	95/156			0.79	1.6	3.9	0.79	4
de Andres et al[13]	50	36.6	20/30	2.3	0			42	36.6 (19, 65)	17/25	9 (2–30)		0	0			5
Bidot et al[15]	21			0	76.1	4.7	0	24	23 ± 3.5	4/20		17/7	0	0	0	58.3	4
Szmyrka-Kaczmarek et al[16]	30	38 ± 11	14/71	1.1	13.3	0	3.3	85	38 ± 11	14/71	8.7 ± 7.1		1.1	0	20		4
Koudrivtseva et al[17]	60	48 ± 10		5	6.6	0	1.6	100	44 ± 10.2		11.8 ± 9.6	26/58	0	1	0	9	5
Shor et al[18]	237			3.06	2.1	8	5.4	96	45 ± 10.3	23/75	12.4 ± 8		5.4	15.6	0	3.1	5
Filippidou et al[29]	92	52 ± 17	37/55	1.1	1.1	0	0	127	51 ± 12	38/89		5/122	21.2	18.1	2.3	4.7	7
	IS							MS									
Colaco et al[19]	10			0	10			17					0	29			4
Roussell et al	126			8.7	0.7	4.8	2.4	89	42 ± 10.5	22/67			16.9	21.4	2.2	13.5	4
Damoiseaux et al[21]	253			1.5	2.1			325					3.69	7.6			5
Iong et al[22]	220			15.9	7.7			90		35/55			5.5	0			6
CSF studies	SLE							MS									
Marchiori et al[26]	10	30.1 ± 11.9		50	0			33					45		6		3
Lolli et al[27]	5			40	0			55					5.4		9		3
Baraczka et al[24]	13	45.1 ± 10.3	1/12	0	30.7			22					0		22.7		7

Abbreviations: aCL, anticardiolipin; β_2GPI, beta-2-glycoprotein = I; NO, number; M/F, males/fenales; DD, disease duration; A/R, active/remission; CTR, control; MS, multiple sclerosis; NOS, Newcastle–Ottawa Scale; IS, ischaemic stroke; CSF, cerebrospinal fluid; SLE, systemic lupus erythematosus.

Table 2
Demographics of studies reporting average titres of antiphospholipid antibodies (A) and relapsing and remitting multiple sclerosis (B)

	CTR (No)	Age	M/F	aCL		β_2GPI		MS (No)	Age	M/F	aCL (mean)		β_2GPI (mean)		NOS
				IgG (mean)	IgM (mean)	IgG (mean)	IgM (mean)				IgG (mean)	IgM (mean)	IgG (mean)	IgM (mean)	
(A)															
Rombos et al[23]	210	33		1.32 ± 0.8	1.35 ± 0.5			42	33	28/14	1.01	1.36 ± 0.32			5
Baraczka et al[24]	11	35	1/10	5.4 (1–17.6)	4.5 (1.1–7.9)			22			2.0 (1.5–5.5)	2.3 (0.15–20.3)			7
Carrillo Mora et al[25]	10					6 ± 2.8	4.2 ± 1.8	12	32.9 (17, 51)	5/7			1.93	1.54	6
	REL (No)			aCL		β_2GPI		REM (No)			aCL		β_2GPI		
				IgG (%)	IgM (%)	IgG (%)	IgM (%)				IgG (%)	IgM (%)	IgG (%)	IgM (%)	
(B)															
Mandoj et al[28]	26	40 ± 10	8/18	11.5	2.7	0	26.9	58	44 ± 9	10/48	1.7	1.7	0	1.7	6

Abbreviations: aCL, anticardiolipin; β_2GPI, beta-2-glycoprotein=I; NO, number; CTR, control; MS, multiple sclerosis; NOS, Newcastle–Ottawa Scale; REL, relapsing; REM, remitting.

[24,26,27] for the effect size of these outcomes. With regards to IgG aCL, the pooled prevalence of participants positive for IgG aCL was lower in MS than SLE (16.36% vs 25%, $p = 0.33$) with elevated heterogeneity ($I^2 = 81.77\%$) (Fig. 2F); with regards to IgM aCL the pooled prevalence of participants positive for IgM aCL was also lower in MS than SLE (10.9% vs 14.2%, $p = 0.39$) with no heterogeneity (Fig. 2G).

Multiple sclerosis and serum anti beta-2-glycoprotein I antibodies

Seven studies explored the relationship between IgG anti-beta$_2$glycoprotein-I (aβ_2GPI) and MS [10,14–18,29]: a total of 747 MS patients and 522 controls were available for the effect size of this outcome; the pooled prevalence of IgG aβ_2GPI positive patients was lower in MS than controls (0.93% vs 4.02%, $p = 0.7$) with high heterogeneity ($I^2 = 53.92\%$) (Fig. 3A). The exclusion of three studies containing amongst cases a mixture of active and inactive MS phenotypes (15, 17, 29) reduced the pooled significance (OR = 0.506; 95% CI: 0.109–2.348; $p = 0.18$) and increased the heterogeneity ($I^2 = 37.91\%$).

Seven studies explored the relationship between IgM aβ_2GPI and MS [10,14–18,29]; a total of 745 MS patients and 522 controls were available for the effect size of this outcome. The prevalence of IgM aβ_2GPI positive participants was similar in the two groups (7.24% vs 6.13%, $p = 0.2$) with elevated heterogeneity ($I^2 = 52.85\%$) (Fig 3B). The exclusion of three studies containing a mixture of active and inactive MS patients [15,17,29] did not alter the pooled OR (1.526, 95% CI: 0.537–4.335) but reduced the heterogeneity ($I^2 = 39.29\%$).

Multiple sclerosis and other serum antiphospholipid antibodies

Four studies investigated the relationship between anti-prothrombin antibody (aPT) of either isotype and MS [10,14,17,18]: a total of 511 MS patients and 379 were available for the effect size of these outcomes. The pooled prevalence of IgG aPT positive participants was lower in MS than controls (2.34% vs 8.44%, $p = 0.9$) with high heterogeneity ($I^2 = 69.82\%$) (Fig. 3C). Removal of the one study combining active and inactive MS patients amongst cases [17] did not alter significance (OR = 0.532; 95% CI: 0.079–3.667; $p = 0.5$) but reduced the heterogeneity ($I^2 = 29.82\%$). The pooled prevalence of IgM aPT positive participants was also lower in MS than controls (5.4% vs 10.6%, $p = 0.6$) with elevated heterogeneity ($I^2 = 76.61\%$) (Fig. 3D). Removal of the one study combining active and inactive MS patients amongst cases [17] did not alter significance (OR = 0.55; 95% CI: 0.160–1.889; $p = 0.34$) but reduced the heterogeneity ($I^2 = 11.34\%$).

Multiple sclerosis and lupus anticoagulant

The lupus anticoagulant was investigated in four studies [23–25,28] but neither patients nor controls had any positive lupus anticoagulant tests.

Direct comparison of antiphospholipid antibodies between active/relapsing vs stable/remission multiple sclerosis

Five studies investigated the relationship between IgG aCL and disease status in MS [12,15,17,28]: a total of 100 active/relapsing MS patients and 206 stable/remission MS patients were available for the effect size of this outcome. The pooled prevalence of IgG aCL positive patients was similar between the two groups (19% vs 18.9%) with no heterogeneity (Fig. 4A). Five studies investigated the relationship between IgM aCL and disease status [9,12,15,17,28] totalling 84 active/relapsing and 200

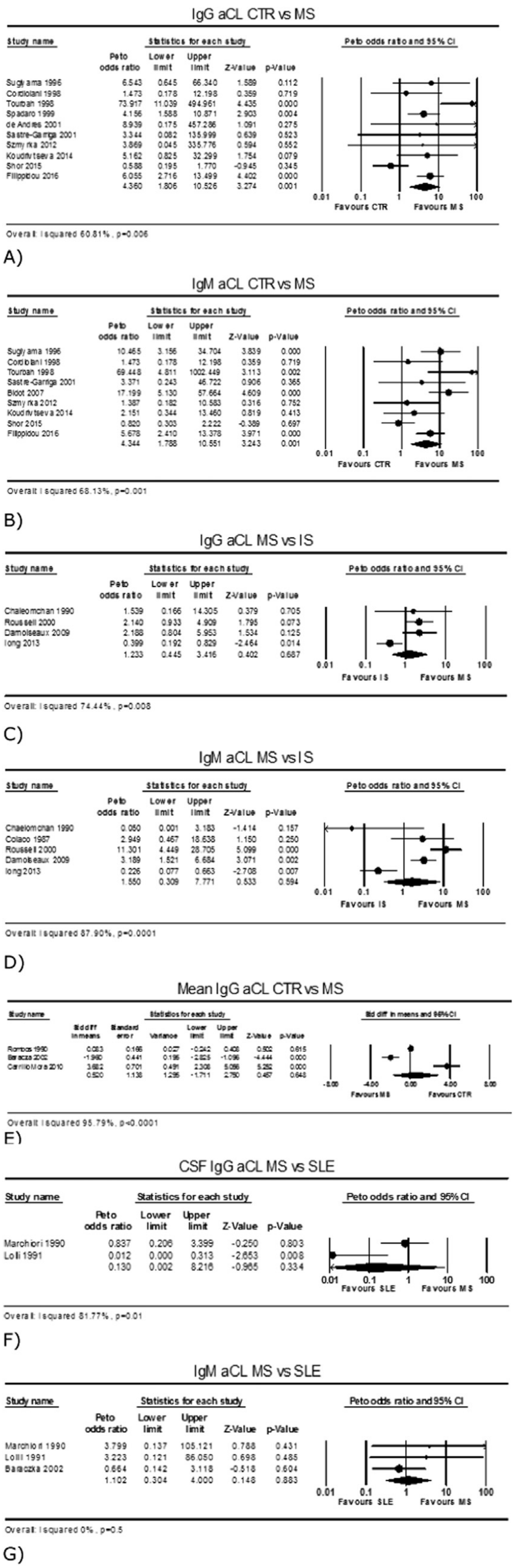

Fig. 2. Forest plots of the effect size of anticardiolipin antibodies in the populations under study. Abbreviations: aCL, (anticardiolipin); MS, multiple sclerosis; CTR, healthy controls; IS, ischaemic stroke; CSF, cerebrospinal fluid; SLE, systemic lupus erythematosus.

stable/remission MS patients for the effect size of this outcome. The pooled prevalence of MS patients positive for IgM aCL was higher in active/relapsing than in stable/remission group (36.9% vs 21%, $p < 0.0001$) with no heterogeneity (Fig. 4B).

Three studies investigated the relationship between aβ_2GPI of either IgG or IgM isotype and disease status totalling 69 active/relapsing MS and 123 stable/remission MS patients for the effect size of these outcomes [15,17,28].

The pooled prevalence of IgG β_2GPI was higher in the active/relapsing than inactive/remission group (20.2% vs 1.6%, OR = 10.169, 95% CI: 1.635–63.256, $p < 0.01$) with no heterogeneity but only one study contributed positive data.

The pooled prevalence of MS patients positive for IgM β_2GPI was much higher in the active/relapsing than inactive/remission group (40.5% vs 3.2%, $p < 0.0001$) with no heterogeneity (Fig. 4C).

Discussion

The case–control studies included in the meta-analysis span more than 2 decades during which different aPL were characterised and evaluated in different MS populations. With regards to IgG and IgM aCL the pooled prevalence of MS patients positive for these antibodies was quite low and despite significant pooled ORs the heterogeneity was very wide.

Several authors compared the prevalence of patients positive for aCL in MS and IS given the link between aCL and thrombosis [3]: pooled data those studies failed to demonstrate a relationship between aCL of either isotype and MS. Similarly, other authors evaluated the prevalence of aCL in the cerebrospinal fluid of MS patients employing SLE patients as disease controls [24,26,27]: neither IgG aCL nor IgM aCL related to MS via this alternative approach.

The suggestion that anti-β_2GPI might be involved in neuroinflammation [36] prompted several surveys assessing the role of this autoantibody in MS: the meta-analysis refuted a link between MS and IgG/IgM aβ_2GPI and also with IgG/IgM aPT.

However, once case–control studies were sub-grouped according to the presence or absence of a mixture of active and inactive MS phenotypes amongst cases it became obvious that those studies including active and inactive MS phenotypes contributed to the wide heterogeneity seen across the all different aPL investigated.

A meta-analysis was therefore performed on those studies that specifically compared active/relapsing vs stable/remission MS and found that the prevalence of patients positive for IgM aCL and IgM aβ_2GPI was significantly greater in active/relapsing MS with no heterogeneity. It is known that natural autoantibodies against oxidated and nitrated lipid moieties emerge during active neurovascular damage [37–40] and it is likely that IgM aCL and IgM aβ_2GPI may indeed represent natural autoantibodies that may have a protective role against disease progression [41].

Indeed a prospective study on 100 MS patients presenting with chronic progressive myelopathy or spinocerebellar syndrome followed up for an average of 21 months supports this contention: the 20% of patients persistently positive for aCL run a milder course than aCL negative patients [42]. Similarly another two prospective studies on 15% of 285 [43] and 5% of 137 MS [44] patients positive for aCL over a period of 1 year did not present with clinical features different from those MS patients that were aCL negative.

The limitations of the meta-analysis reflect the average quality of the studies included that prevented OR adjustments by age, sex,

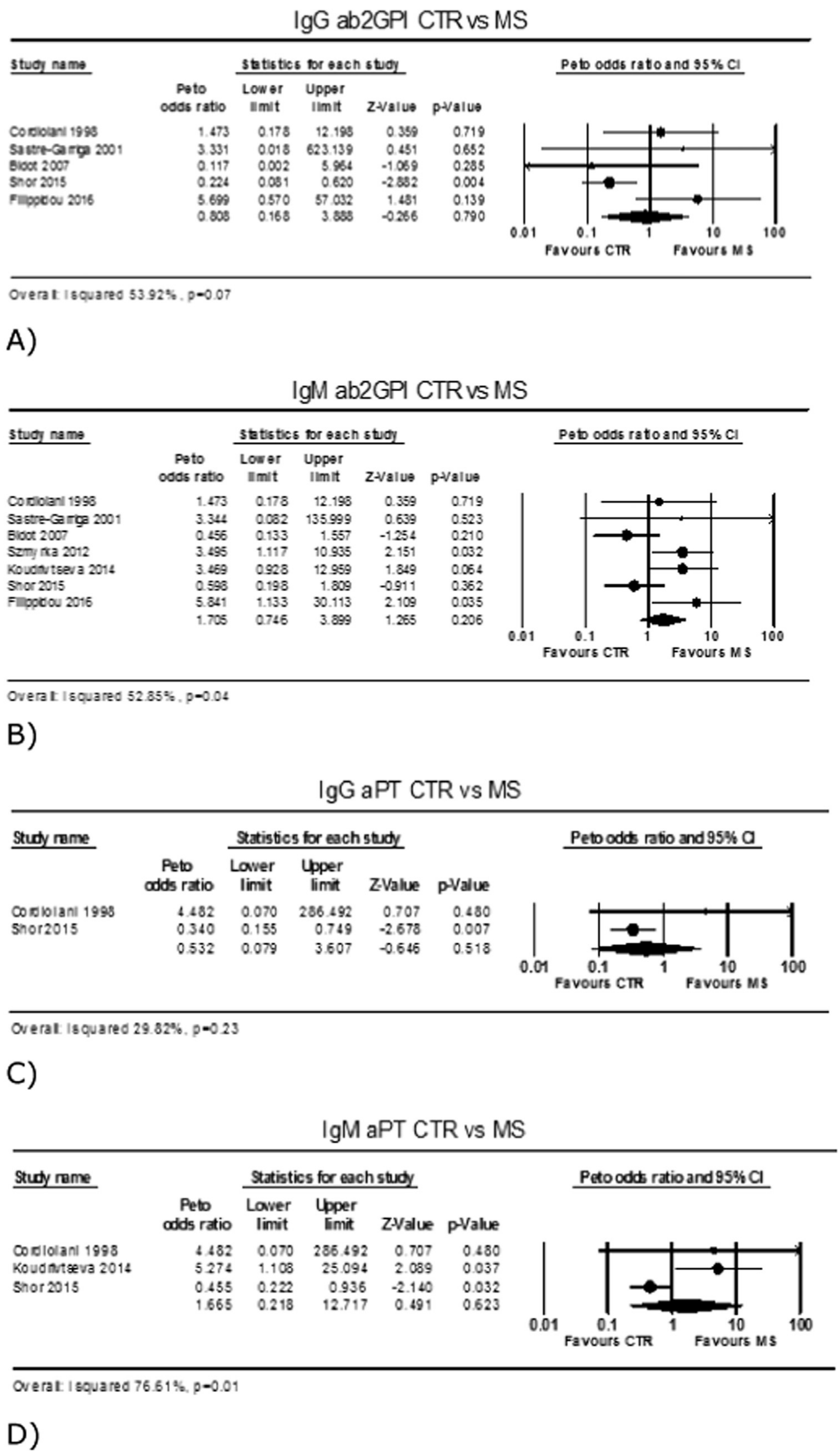

Fig. 3. Forest plots of the effect size of anti-beta$_2$glycoprotein-I (aβ_2GPI) and anti prothrombin (aPT) in the populations under study. CTR, healthy controls; MS, multiple sclerosis.

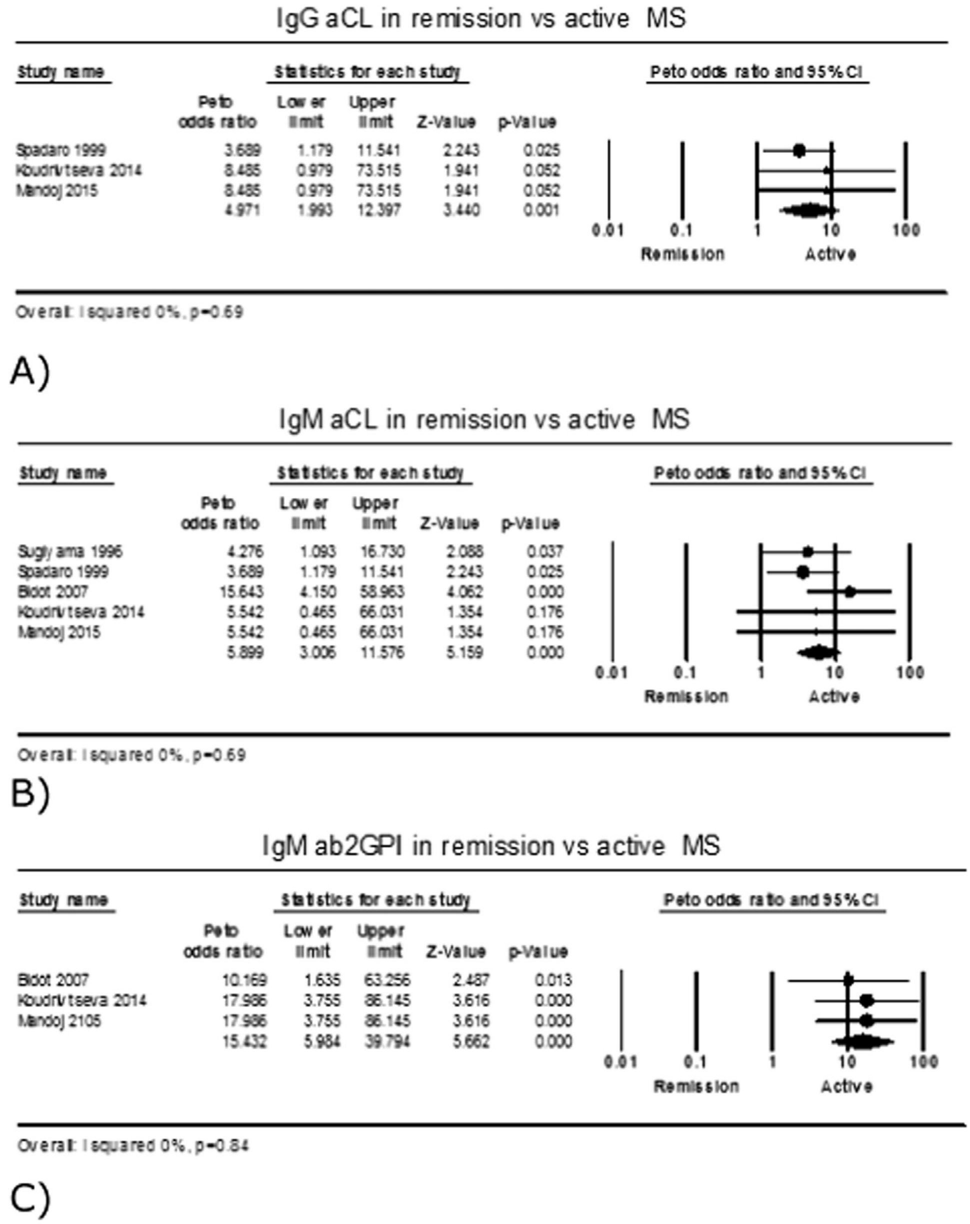

Fig. 4. Forest plots of the effect size of anticardiolipin (aCL) and anti-beta$_2$glycoprotein-I (aβ_2GPI) antibodies in remission and active multiple sclerosis.

and disease duration. The different tests for aPL, the different diagnostic criteria for MS, the variety of MS phenotypes and their disease activity may have contributed to the wide heterogeneity found: indeed we have shown that studies combining active and inactive MS amongst cases accounted for a large part of the heterogeneity that was mitigated or disappeared after subgroup analysis.

But the major limitation of the meta-analysis was the lack of reporting aPL titres that in most cases were measured only once: almost all studies compared the percentage of aPL positive participants between MS and controls. The four studies that reported mean aPL levels showed that they were well below the thrombogenic cut-off of 40GPL and none of the MS patients in these studies had suffered any vascular occlusion [23–26]. A more recent study reported average serum levels of aCL and on positive patients only with individual values above 40GPL but all MS patients were aβ_2GPI negative and did not suffer thrombosis [29].

Conclusion

Our meta-analysis refutes a link between aPL and MS. The strong relationship between IgM aPL and active/relapsing MS may represent either an epiphenomenon of active neuro-inflammation or natural autoantibodies against oxidative epitopes recently described in MS [45,46] and may protect against a more severe disease course [42].

To investigate a potential role for older and newer aPL in MS a more rigorous approach is needed in order to set up adequately powered prospective cohorts of MS patients divided by phenotypes, where persistent aPL titres are reported and related to disease activity/severity and outcomes. This will generate more consistency across studies that may lead to better understanding of a possible role for aPL in the pathogenesis and management of aPL positive MS and help clinicians in deciding whether any adjunct anticoagulation is required in MS patients positive for aPL. Until such data are available it remains to the clinician's judgement to perform a risk factor assessment to decide whether to offer primary thromboprophylaxis in a disorder like MS where the trombotic risk is greater than the general population [47].

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