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The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: a systematic review

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Abstract

Background Around 10% of all thrombotic cerebrovascular events (CVE) occur in young population and in a large proportion of those the trigger remains undetermined. Antiphospholipid antibodies (aPL) are recognised risk factors for ischaemic stroke and recurrent thrombotic events; however, the frequency of aPL in young people with CVE is still an unresolved issue.

Objectives To estimate the frequency of aPL in young adults with CVE and to determine whether aPL-positive young individuals are at greater risk of CVE when compared with individuals without aPL by systematically reviewing the literature.

Methods Medline reports published between 1970 and 2013 investigating the presence of aPL in young patients (<50 years old) with CVE were included. The median frequency for positive aPL, including lupus anticoagulant, anticardiolipin antibodies (aCL) and antibodies against β2Glycoprotein I (anti-β2GPI), was calculated for stroke and transient ischaemic attacks.

Findings This systematic review is based on available data from 5217 patients and controls from 43 studies analysing the frequency of aPL in young patients with CVE. The overall aPL frequency was estimated as 17.4% (range 5%–56%) for any CVE, 17.2% (range 2%–56%) for stroke and 11.7% (range 2%–45%) for transient ischaemic attack (TIA). The presence of aPL increased the risk for CVE by 5.48-fold (95% CI 4.42 to 6.79). Based on available data, the frequency of aPL in young patients with CVE can be estimated at 17%, rising up to 22% for aCL in patients with stroke. The presence of aPL seems to confer a fivefold higher risk for stroke or TIA when compared with controls. However, variability in test reproducibility and cut-off definition still represent an important methodological limitation for the current diagnostic testing for aPL. These observations should be confirmed by appropriately designed population studies.

Introduction

Around 10% of all thrombotic cerebrovascular events (CVE) occur in young population defined as younger than 50 years old;1 in the majority of these patients, the cause of the ischaemic stroke remains undetermined.[2]

Arterial thrombosis is a major clinical manifestation of the antiphospholipid syndrome (APS), an autoimmune condition characterised by thrombotic events and/or pregnancy morbidity with persistently positive antiphospholipid antibodies (aPL).3 Considering all patients with cerebral ischaemia, the prevalence of aPL seems rather high in young adults,4 who might constitute a subgroup at high risk for recurrence.

Very recently, through the support of the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION), a systematic review aiming to estimate the frequency of clinically significant aPL profiles in the general population (no age limit) was completed. This study revealed that aPL (by any criteria test) are seen in approximately 14% of individuals with stroke.[5]

In patients with CVE aged <50, however, the prevalence of aPL and the risk for CVE associated with these aPL are still being inconsistently reported. Therefore, the primary objective of this study was to estimate the frequency of aPL in young adults (<50 years old) with CVE. The second goal was to determine whether aPL-positive young individuals have a greater risk of an episode of ischaemic stroke when compared with individuals without aPL.

METHODS

Literature search

A detailed literature search strategy has been developed a priori. Key words and subject terms used in the search included: 'stroke' [MeSH Terms] OR stroke [Text Word], '('arteries' [MeSH Terms] OR 'arteries' [All Fields] OR 'arterial' [All Fields]) AND ('thrombosis' [MeSH Terms] OR 'thrombosis'[All Fields]);' 'antibodies, anticardiolipin' [MeSH Terms] OR ('antibodies' [All Fields] AND 'anticardiolipin' [All Fields]) OR 'anticardiolipin antibodies' [All Fields] OR ('anticardiolipin' [All Fields] AND 'antibodies' [All Fields]);' and 'antibodies, antiphospholipid' [MeSH Terms] OR ('antibodies' [All Fields] AND 'antiphospholipid' [All Fields]) OR 'antiphospholipid antibodies' [All Fields] OR ('antiphospholipid' [All Fields] AND 'antibodies' [All Fields])', 'lupus coagulation inhibitor' [MeSH Terms] OR ('lupus' [All Fields] AND 'coagulation' [All Fields] AND 'inhibitor' [All Fields]) OR 'lupus coagulation inhibitor' [All Fields] OR ('lupus' [All Fields] AND 'anticoagulant' [All Fields]) OR 'lupus anticoagulant' [All Fields]', anti-beta [All Fields] AND 2 [All Fields]

The search strategy was applied to Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present. The grey literature was searched by applying a similar strategy to Google Scholar, PubMed and the Proquest Dissertation and Theses databases. Additional references were identified from manual review of the reference lists of included articles.

Study selection

Potential studies identified with the above search strategy were exported to an electronic reference management software program (RefWorks V.2.0). Duplicate studies were identified and removed using the filter functions 'exact duplicates' and 'close duplicates. Two independent reviewers (SS

and MLB) reviewed all potential studies. Eligibility was first determined by review of the title and abstract and then by full article review. Disagreements were resolved by consensus; if consensus was not achieved, a third party (GS or MK) provided an assessment of eligibility. As the data on eligibility were dichotomous (eligible: yes/no), inter-rater agreement at both the title and abstract review and the full article review stages were determined by calculation of Cohen's κ coefficient.[6]

Inclusion and exclusion criteria

A study was included if (1) it reported on the laboratory investigation of any aPL and confirmed CVE (2) included patients aged <50 years. A study was excluded if no information about the age of included patients was given. Review articles, case report and case series with a sample size of five or fewer were excluded from the analysis.

Risk of bias assessment

Two reviewers independently assessed the risk of bias of individual studies using the Newcastle–Ottawa Scale (NOS) for cohort studies, and the NOS for case control studies when appropriate. The NOS is a scoring tool used to assess quality of evidence and risk of bias for non-randomised studies included in meta-analyses. This tool is chosen as its face and content validity as well as its inter-rater reliability has been well established.[7]

The criterion validity and intra-rater reliability of this tool were actively determined. The overall quality of evidence was determined using GRADE criterion and summarised using GRADE profiler.

Risk of publication bias assessment

To assess publication bias, a visual review of the symmetry of the funnel plot was performed. The limitations of using the funnel plot for the assessment of publication bias (particularly in a topic area with relatively few, relatively small publications) were also considered.

Data extraction

All the papers were scrutinised for the following: (1) study design (retrospective, prospective, case-control, cross-sectional and case series); (2) number of patients, sex and age (mean, range); (3) type of outcome; (4) number and type of aPL tests used (criteria tests vs non-criteria);8 (5) definition of 'positive criteria aPL' (low, medium or high titre, or other) as per the study's definition; (6) confirmation of criteria aPL, at least 6 weeks9 or 12 weeks8 apart; and (7) frequency of positive aPL in the study population (defined by sex and age range).

Data were explored to determine if sources of heterogeneity could be explained by the following a priori hypotheses: study design (cohort vs case-control); reported medical comorbidities in the patient population; and the aPL type and methods used for laboratory aPL testing (including the number of aPL tests performed). Indeed, we can hypothesise that each of these subgroup analyses could account for potential heterogeneity in the pooled estimate.

Statistical analysis

Inter-rater agreement was determined using a Cohen's κ online calculator. A κ value between 0.40 and 0.59 will be considered fair agreement; 0.60 and 0.74 will be considered good agreement; and

≥0.75 will be considered excellent agreement. Software such as Review Manager can be used for generating forest plots and the funnel plot.

Given the non-parametric distribution of our data, we expressed aPL frequency as median (range). First, we calculated the frequency of aPL positivity of any aPL test. When possible, the frequency was estimated for each of the aPL criteria test (anticardiolipin antibodies (aCL), anti-β2GPI and lupus anticoagulant (LA)) and non-criteria aPL tests (antibodies against prothrombin, phosphatydilserine, phosphatidylinositol, phosphatydilethanolamine). We then estimated the overall frequency of the three aPL criteria tests separately for studies confirming aPL positivity between 6 and 12 weeks apart versus studies completed without aPL confirmation. Prospective versus non-prospective studies (case series, retrospective, case-control and cross-sectional) were also analysed.

When reported, ORs with 95% CI (OR (95% CI)) for CVE were recorded. When not available, they were calculated, if possible, by means of contingency tables. In case-control and cross-sectional studies, contingency tables were used to compare the proportion of aPL in patients with and without CVE. In prospective studies, contingency tables were established as previously reported.[10,11] Briefly, when CVE was the enrolment criterion, the OR (95% CI) was calculated by comparing the proportion of aPL in patients with or without recurrent CVE during follow-up. When positivity for aPL was the enrolment criterion, the OR (95% CI) was calculated by comparing the rates of CVE during follow-up of patients grouped, if possible, according to different antibody type and titres.

Results

A total of 840 citations were identified through the literature search from January 1970 to September 2013. A schematic representation of the results of the search strategy is given in figure 1. A total of 43 articles assessing the frequency of aPL in patients aged <50 years with CVE (stroke and/or transient ischaemic attack (TIA)) were retrieved.[4,12–54] As per inclusion criteria, all the studies enrolled patients aged <50 years, with a median age of 37 (range 16–50). Overall, all studies included gave information on 3349 patients and 1868 controls. While most of the studies were of a retrospective design, six prospective studies contributed with 408 patients.[4,1,2–16] Table 1 summarises the characteristics of the included studies. Subgroup analysis aiming at estimating whether aPL-positive young individuals have a greater risk for CVE when compared with individuals without aPL was possible in 15 studies.[4,9,12-15,17,18,22,24,31,33,37,47,54.]

Concomitant thrombotic risk factors for CVE were reported in 88% of the studies. However, the role of these risk factors was statistically evaluated in only a minority of the studies and reported by very heterogeneous methods, either in terms of the selection of the stated risk factor, their definition and the outcome. This approach limited the possibility of further multivariate adjustments when analysing the aPL-induced risk.

All the studies were performed in patients without a concomitant autoimmune disease. However, nine cases out of 3349 (0.26%) were diagnosed as having systemic lupus erythematosus after further evaluation following or in concomitance with the CVE episode.

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Estimated frequency of aPL in young patients with CVE

Table 2 reports the median (range) values for aPL frequency, subgrouped according to the type of aPL (aCL, anti-β2GPI, LA and non-criteria aPL). The overall aPL frequency was estimated as 17.4% (range 5–56) for CVE, 17.2% (range 2–56) for stroke and 11.7% (range 2–45) for TIA. When subanalysing studies with and without the aPL positivity confirmation by retesting between 6 and 12 weeks apart, the overall aPL frequency was 17.2% (range 2–55) and 18.02% (range 3–55), respectively (table 3).

As expected, although not statistically significant, a tendency for lower frequency of aPL was found in prospective studies when comparing with non-prospective ones (10.31% (range 3–42) and 18.92% (range 2–59), respectively).

Risk estimation for CVE in aPL-positive young individuals

The OR (95% CI) of aPL for CVE was analysed in 15 studies on 1081 patients and 1868 controls (figure 2). Overall, 13 out of 15 studies (86.6%) reported significant associations between aPL and CVE, with a cumulative OR of 5.48 (95% CI 4.42 to 6.79). Only two studies failed to confirm the association between any aPL and CVE.[19 ,29]

Discussion

CVE are one of the leading causes of mortality, with a reported annual 6 million fatal events worldwide.1 While stroke mainly affects elderly people, yet approximately 10% occurs in patients aged 50 or less.55 Despite these alarming figures, limited data exist on the frequency of other non-conventional risk factors in young population affected by CVE.

In this study, we estimate that aPL, by any test included in the classification criteria,8 are positive in approximately 17% of patients with CVE under the age of 50. Among these aPL, aCL seems to be the more frequently detected, with an estimated frequency of 22% in young patients with stroke. This is the first comprehensive systematic analysis of studies investigating the association of aPL with CVE in young patients aged <50 years. In contrast to Bushnell and Goldstein,56 we have included in the statistical model only those studies that focused solely and exclusively on young adults.

Recently, Andreoli *et al*,57 in another work on behalf of the APS ACTION, investigated the frequency of aPL in the general population with pregnancy morbidity, stroke, myocardial infarction and deep venous thrombosis, providing the first attempt to evaluate the prevalence of aPL in patients experiencing APS-related clinical manifestations. These authors estimated aPL positivity in around 13.5% of individuals with stroke. However, their analysis involved a very wide age population ranging from 11 to 92 years old.57 In our study where young adults, a subgroup at high risk for recurrence,4 were analysed, we found a higher frequency ranging from 15% for anti-β2GPI to 22% for aCL and a strong association between aPL and CVE.

Overall, our results support the concept that aPL could be considered a leading cause of CVE in young adults. However, robust scientific data from large controlled population studies to support this statement are still lacking. An important limitation to our analysis is that adequate controls groups, crucial for the calculation of risk estimation, were available for only a few studies.[4,9,12–15,17,18,22,24,31,33,37,47,54] Moreover, among these, the results of studies with less than 30 patients produced quantified OR with wide CIs and poor test accuracy as expected.[58] Variability in test reproducibility and cut-off definition represent an important methodological limitation for the current diagnostic testing for aPL (table 1). In our systematic review, we observed that both aCL and anti-β2GPI assays were widely heterogeneous with respect to reporting the cut-off for 'aPL positivity.' Approximately 60% of the papers that related to aCL used a low cut-off value (<20 units) for the definition of positive results. Such a cut-off does not allow stratifying those medium- to high-titre patients who would fulfil laboratory criteria according to the international consensus.[8] Only about 30% of the cited studies included the confirmation of aPL, a step strongly recommended for classification. Moreover, the potential for inter-laboratory variability was not addressed.[59] On the basis of these methodological issues, the risk assessment post-test probabilities calculated in this study should be viewed as rough estimates rather than precise calculations. However, current evidence supports the concept that the presence of aPL itself is a risk factor rather than a diagnostic marker and the risk of thrombosis progressively increases with the increase in number of positive aPL tests, regardless of the titre.[60–63]
This new concept, once validated in prospective studies, might enrich the clinical workup in terms of risk assessment, patient stratification, prognosis and, hopefully, therapeutic approach.

We acknowledge that our study has some limitations. First, despite the systematic nature of this review, combining heterogeneous studies (ie, those from varying patient populations) leads to shortcomings in the interpretation of the results. Including only studies from unselected ischaemic stroke patients would have provided conclusions that are, perhaps, more generalisable. However, this combination of aPL prevalence studies from both selected and unselected patients provided us with larger numbers for meaningfully calculating the estimates, making a stronger case. Second, the information that could potentially increase the accuracy of the risk estimation, including adjustments for clinical or historical factors, physical examination findings, and other diagnostic test results, was rarely reported in the analysed studies, impeding the assessment about a potential direct causal relationship between aPL and the clinical outcomes.

In conclusion, this study estimates that the frequency of aPL in young patients with CVE is 17%, increasing up to 22% for aCL in patients with stroke. The presence of any aPL seems to confer a fivefold increased risk for stroke or TIA when compared with controls without aPL. Evaluating the thrombotic risk by including aPL testing can potentially lead to a substantial change in the management and, more critically, in the prognosis of these patients. Undoubtedly, these observations should be confirmed with appropriately designed population studies.

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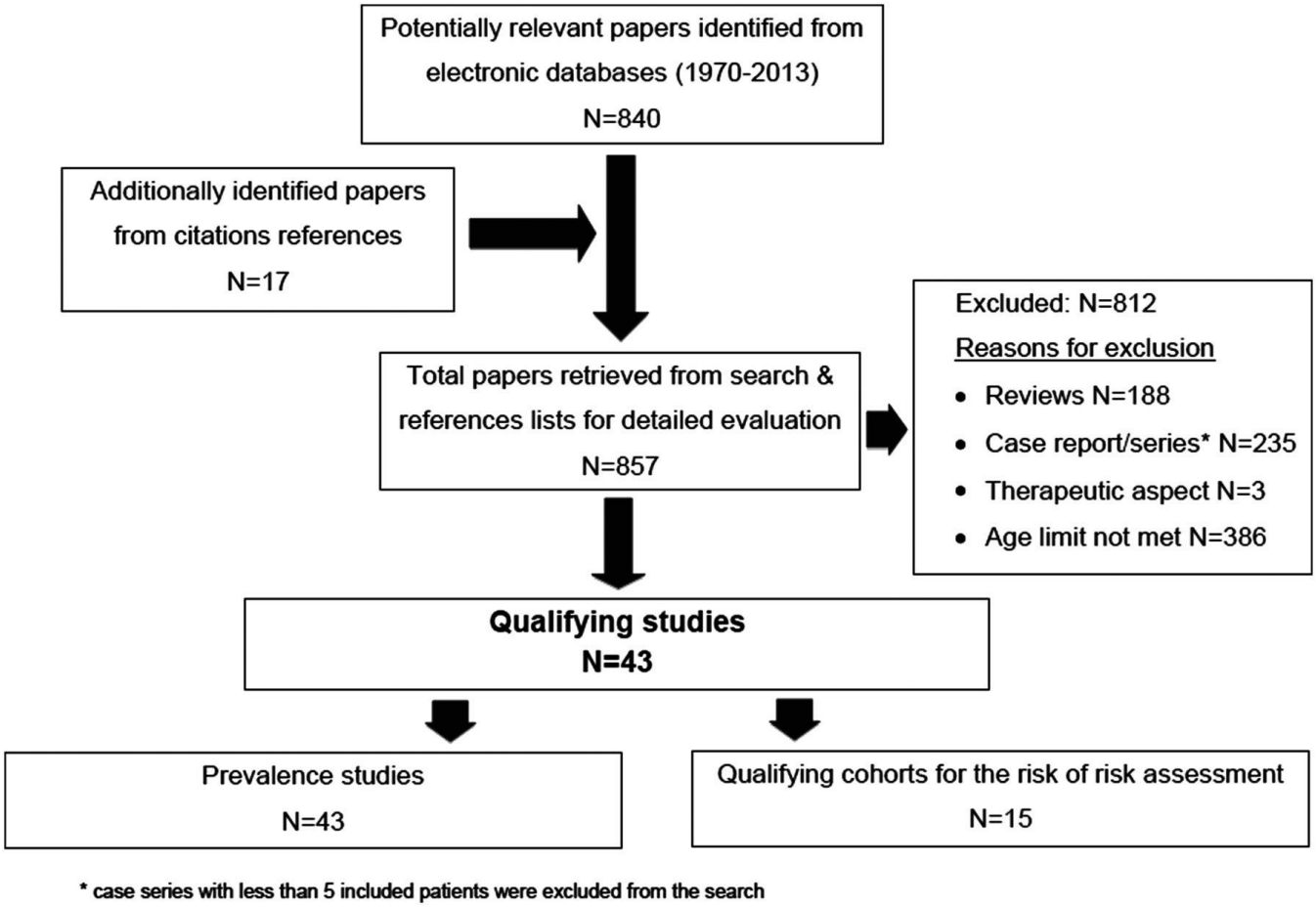

Figure 1

Literature search strategy on the association between antiphospholipid antibodies and cerebrovascular events.

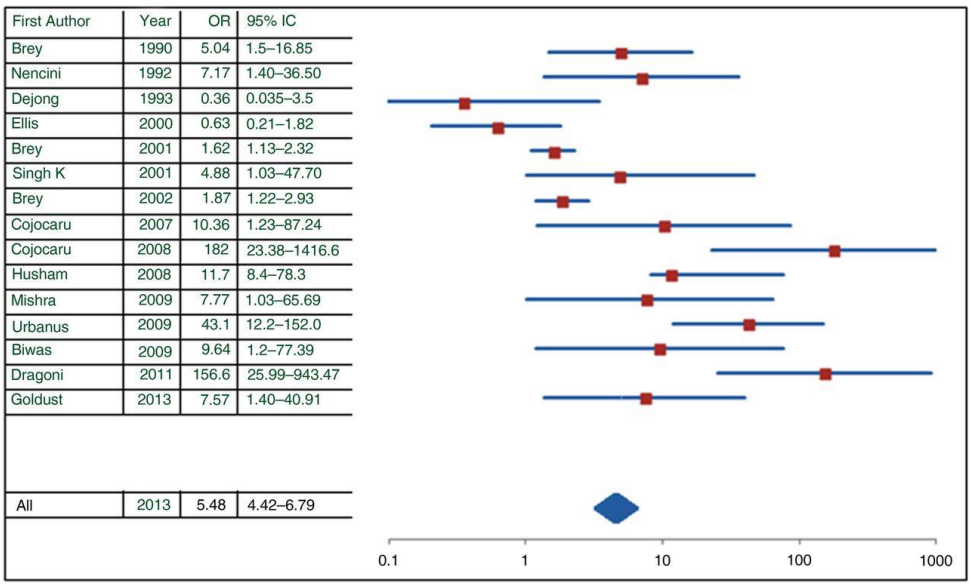

Figure 2

Association between antiphospholipid antibodies and cerebrovascular events.

Table 1

Characteristics of the literature on aPL frequency in young people with CVE

		N=43 (patients)	%
Publication year	48.8% between 1984 and 2000		
Definition of aPL positivity cut-off	10–19 U*	25* (1975)	58.14
	20–39 U*	4* (309)	9.30
	99th percentile	2 (214)	4.65
	Not reported	12 (851)	27.91
Confirmation of aPL 6–12 weeks apart		15 (732)	34.88
Design of the study	Retrospective cohorts/cross-sectional/case series	25 (2190)	58.14
	Case-control studies	12 (751)	27.91
	Prospective studies	6 (408)	9.30
Presence of control group		15 (1081)	34.88
Evaluation of concomitant cardiovascular risk factors†		38 (2789)	88.30
Autoimmune disease		4 (9)	9.30

*17/30 (56.6%) defined as IgG anti-phospholipid units (GPL)/IgM anti-phospholipid units (MPM).
†At least one of the following: smoking, hyperlipidaemia, hypercholesterolaemia, arterial hypertension or diabetes.
aPL, antiphospholipid antibodies; CVE, cerebrovascular event; N, Number of studies.

Table 2

The frequency of any aPL, aCL, anti-β2GPI, LA test and non-criteria aPL combined in patients with different CVE outcomes

	aPL		aCL IgG/M		anti-β2GPI IgG/M		LA		Non-criteria aPL*	
CVE	N	Median*	N	Median*	N	Median*	N	Median*	N	Median†
CVE (any)	43	17.4 (2–56)	39	18.2 (3–35)	8	13.7 (5–28)	30	15.4 (0–26)	6	14.9 (7–27)
Stroke	38	17.2 (2–56)	37	22.0 (3–35)	8	13.7 (5–28)	28	15.8 (0–26)	6	14.9 (7–27)
TIA	13	11.7 (2–45)	12	12.7 (0–23)	0	–	10	13.42 (7–19)	2	3 (2–4)

*Median is given as median % (range).
†Antiprothrombin antibodies N=3; antiphosphatidylethanolamine antibodies N=1; antiphosphatidylinositol antibodies N=1; antiphosphatidylserine antibodies N=1; N: number of studies.
aCL, anticardiolipin antibodies; anti-β2GPI, anti-β2-glycoprotein I antibodies; aPL, antiphospholipid antibodies; CVE, cerebrovascular event; LA, lupus anticoagulant; TIA, transient ischaemic attack.

Table 3

The overall frequency of criteria antiphospholipid antibodies (aPL) analysed for aPL confirmation and study design

Overall criteria aPL frequency							
aPL confirmation							
Yes		No		Prospective studies		Non-prospective studies	
N	Median % (range)	N	Median % (range)	N	Median % (range)	N	Median % (range)
13	17.2 (2–55)	30	18.02 (3–55)	6	10.31 (3–42)	37	18.92 (2–59)

N, number of studies.