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Viral hepatitis and anti-phospholipid antibodies positivity: A systematic review and meta-analysis

Pasquale Ambrosino[a], Roberta Lupoli[a], Paolo Tarantino[a], Alessandro Di Minno[a], Luciano Tarantino[b,1], Matteo Nicola Dario Di Minno[a,c,*,1]

[a] Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy
[b] Department of Surgery, Interventional Hepatology Unit, Andrea Tortora Hospital, Pagani, Italy
[c] Unit of Cell and Molecular Biology in Cardiovascular Diseases, Centro Cardiologico Monzino, IRCCS, Milan, Italy

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ABSTRACT

Background: Anti-phospholipid antibodies positivity is associated with several clinical conditions, including infectious diseases.
Aims: We performed a meta-analysis evaluating the association of hepatitis B and C with anti-phospholipid antibody positivity and with anti-phospholipid antibody-related thrombotic complications.
Methods: Studies evaluating the association of viral hepatitis with anti-cardiolipin, anti-β_2 glycoprotein-I and lupus anticoagulant antibodies and anti-phospholipid antibody-related thrombotic events were systematically searched.
Results: 20 studies (2319 cases, 1901 controls) were included. The analyses showed that viral hepatitis is associated with the presence of anti-cardiolipin and anti-β_2 glycoprotein-I antibodies. The association with anticardiolipin antibodies was confirmed in both hepatitis B (OR 11.22, 95% CI: 6.68–18.84) and hepatitis C (OR 11.26, 95% CI: 6.82–18.59). Similarly, compared to controls, anti-β_2 glycoprotein-I antibodies were found more frequently in hepatitis B (OR 14.07, 95% CI: 3.06–64.66) and hepatitis C (OR 5.64, 95% CI: 1.69–18.77). Moreover, 11 studies (257 cases, 1079 controls) showed a higher prevalence of venous and/or arterial thrombosis in patients with hepatitis and anti-cardiolipin antibody positivity compared hepatitis alone (OR 3.29, 95% CI: 1.79–6.07). This result was consistently confirmed in hepatitis C (OR 3.64, 95% CI: 1.78–7.46) but not in hepatitis B.
Conclusions: Viral hepatitis is significantly associated with anti-phospholipid antibody positivity and with anti-phospholipid antibody-related thrombotic complications.

1. Introduction

The anti-phospholipid syndrome (APS) is an acquired autoimmune disease characterized by the presence of anti-phospholipid antibodies (aPL) in patients with history of venous or arterial thrombosis and/or recurrent miscarriages [1,2]. aPL are a heterogeneous group of autoantibodies with an affinity for anionic phospholipids [3]. They include anticardiolipin (aCL), anti-β_2 glycoprotein-I (anti-β_2GPI), and lupus anticoagulant (LA) antibodies [4]. Prevalence of aPL in the general population ranges between 1% and 5%, but only a minority of aPL-positive subjects develops APS [5]. It has been reported that the prevalence of APS is around 40–50 cases per 100000 persons [6].aPL positivity has been associated with a variety of clinical conditions, including rheumatic autoimmune diseases, malignancies, and infectious diseases [7]. Since the association of aPL and syphilis was first described [8], many other infectious diseases, particularly of viral origin, have been associated with aPL positivity [9,10] and aPL-related thrombotic complications [11–14].

Hepatotropic viruses, in particular hepatitis B (HBV) and hepatitis C (HCV) virus, are the most common cause of chronic infectious hepatitis worldwide [10]. During recent years, growing interest has been given to the relationship between these viruses and aPL positivity. In particular, several studies documented higher prevalence of these autoantibodies in both HBV- [15,16] and HCV-infected patients [17,18]. Moreover, an association between viral hepatitis and aPL-related thrombotic complications has been also documented [19], suggesting that aPL may not only be an epiphenomenon of the infectious process but they may also play a

* Corresponding author at: Department of Clinical Medicine and Surgery, Federico II University, Via S. Pansini 5, 80131 Napoli, Italy. Tel.: +39 081 7462060; fax: +39 081 7462060.
E-mail address: dario.diminno@hotmail.it (M.N.D. Di Minno).
[1] These authors share co-seniorship of this study.

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pathogenic role. However, these data have been challenged in other studies [20,21]. In a previous meta-analysis [22], aCL were found to be significantly more frequent in both HBV- and HCV-infected patients compared to healthy controls (OR 13 and 14, respectively), whereas a trend towards a higher prevalence of anti-β_2GPI – not achieving statistical significance – was found in HCV-infected, but not in HBV-infected subjects. However, the meta-analysis included less than 50% of available studies and did not analyze the risk of thrombotic complications in hepatitis patients with aPL positivity.

The aim of the present study is to perform a systematic review and meta-analysis of case–control and cohort studies evaluating the association of HBV and HCV infections with the prevalence of aPL and aPL-related thrombotic complications.

2. Methods

A protocol for this review was prospectively developed, detailing the specific objectives, the criteria for study selection, the approach to assess study quality, the outcomes, and the statistical methods. The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist [23] was followed for conducting and reporting this review.

2.1. Search strategy

To identify all available studies, a detailed search pertaining to HBV and HCV infection, aPL positivity and aPL-related thrombotic complications was conducted according to PRISMA guidelines [23]. A systematic search was performed in major electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the following search terms in all possible combinations: *hepatitis C*, *hepatitis B*, *viral hepatitis*, *antiphospholipid syndrome*, *antiphospholipid antibodies*, *anti-cardiolipin antibodies*, *anti-beta 2-glycoprotein I antibodies*, *lupus anticoagulant*. The last search was performed on 26th July 2014. The search strategy was developed without any language restriction.

In addition, the reference lists of all retrieved articles were manually reviewed. Two independent authors (PA and MNDDM) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (LT). Discrepancies were resolved by consensus. Selection results are reported according to the PRISMA flowchart (Supplementary Figure S1).

2.2. Data extraction and quality assessment

According to the pre-specified protocol, all studies evaluating the impact of HBV and HCV infections on the prevalence of aPL and aPL-related thrombotic complications were included. Case-reports, case-series without a control group, reviews and animal studies were excluded. The included studies were classified as having a case–control design or a cohort design.

Only HBV and HCV infections were considered in this meta-analysis, while hepatitis A (HAV), hepatitis D (HDV), and hepatitis E virus (HEV) infections were not taken into account. Other viral hepatitis infections (cytomegalovirus, herpes virus, Epstein–Barr virus) were also excluded.

To be included in the meta-analysis, a study had to provide the row number or the percentage of subjects with aCL, anti-β_2GPI, and/or LA positivity. Studies reporting the prevalence of thrombotic events (both venous and arterial) among hepatitis patients with and without aPL positivity were also included.aPL positivity was defined as the positivity of at least one among immunoglobulin A (IgA), immunoglobulin M (IgM) or immunoglobulin G (IgG) directed against phospholipids. Considering that a patient may exhibit the positivity of more than one isotype, when separate data were provided, the higher prevalence was taken into account.

In each study, data regarding sample size, major clinical and demographic variables, presence of aCL, anti-β_2GPI, or LA, and history of thrombosis were extracted.

Given the characteristics of the included studies, the evaluation of methodological quality of each study was performed with the Newcastle-Ottowa Scale (NOS), which is specifically developed to assess quality of observational studies including case–control and cohort studies [24]. The scoring system encompasses three major domains (selection, comparability and exposure/outcome) and a resulting score range between 0 and 8, a higher score representing a better methodological quality.

Results of the NOS quality assessment are reported in Supplementary Table S1.

2.3. Statistical analysis and risk of bias assessment

Statistical analysis was carried out using Review Manager [Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark] provided by The Cochrane Collaboration.

Differences among cases and controls were expressed as OR with pertinent 95% confidence intervals (95% CI).

The overall effect was tested using Z scores and significance was set at $P < 0.05$. Statistical heterogeneity among studies was assessed with chi square Cochran's Q test and with I^2 statistic, which measures the inconsistency across study results and describes the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25–50% moderate, and 50% high heterogeneity [25].

Publication bias was represented graphically by funnel plots of the standard difference in means versus the standard error. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect [26].

In order to be as conservative as possible, the random-effect method was used to take into account the variability among included studies.

2.4. Sensitivity analyses

We repeated sensitivity analyses by including only studies judged as "high quality" according to NOS (i.e. NOS $\geq$ to the median value found among included studies).

Further analysis was performed after excluding studies potentially evaluating the same population as other included studies.

We also planned to perform separate analyses for case–control and cohort studies.

We did not perform any subgroup analyses.

2.5. Meta regression analyses

We hypothesized that the presence of aCL, anti-β_2GPI, and LA positivity may be affected by differences in baseline characteristics of subjects included in different studies (mean age, percentage of male patients). Moreover, we hypothesized that the prevalence of thrombotic complications in hepatitis may be affected also by other clinical variables (thrombocytopenia, cirrhosis, antiviral therapy, HCV-RNA positivity). To assess the possible effect of such variables in explaining the different results observed across studies, we performed meta-regression analyses after implementing regression models with presence of aCL, anti-β_2GPI, and LA, or prevalence of thrombotic events as dependent variables (y) and the