



## Association of psychosis with antiphospholipid antibody syndrome: A systematic review of clinical studies

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### ABSTRACT

**Objective:** In this systematic review, we reviewed the association between Antiphospholipid antibody syndrome (APS) and psychosis and focused on the prevalence, clinical presentation, immunologic and neurological workup, treatment options, and clinical outcomes.

**Methodology:** We performed this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)'s guidelines. We searched eight databases for potential articles and manually searched references and relevant articles of included studies. We included all articles reporting psychotic symptoms in patients with APS. Article quality was assessed using an adapted version of the Cancer Council Australia tool for case-series.

**Results:** We included 23 articles of 454 articles found. The mean patient age at presentation was 39 years and most patients were women. Delusions and hallucinations were the common clinical manifestations of APS-associated psychosis. Findings on neuroimaging were attributed to APS-associated thrombosis in most cases. Most patients had a complete resolution of psychotic symptoms.

**Conclusion:** APS-associated psychosis is rare. Later age of onset for psychosis, sudden onset, female sex, and comorbid medical and psychiatric symptoms should raise the suspicions for the presence of APS. APS-associated psychosis may have a favorable prognosis. However, further studies need to validate this conclusion.

### 1. Introduction

Antiphospholipid antibody syndrome (APS) is an autoimmune disorder first described in the 1980s [1]. While the pathogenesis of APS is still obscure, recent studies suggest a multifactorial pathogenesis involving an interplay between genetic and environmental factors [2]. It is characterized by recurrent thrombosis and/or pregnancy loss in the presence of positive circulating antiphospholipid antibodies [1]. Antiphospholipid antibodies can induce a procoagulant phenotype leading

to an arterial and venous thrombotic manifestation which is typical of APS [2].

APS can be primary without a known cause or secondary due to underlying rheumatologic or autoimmune illness, particularly systemic lupus erythematosus (SLE) [3–4]. A concomitant diagnosis of APS among 20% to 35% of patients with SLE has been suggested [3]. Therefore, assessing anti-phospholipid antibodies is recommended in the initial evaluation of patients with SLE. As an autoimmune condition, APS can affect any organ resulting in thrombophlebitis, deep vein

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thrombosis, Budd-Chiari syndrome, hepatomegaly, elevated liver enzymes, Addison's disease, pulmonary thromboembolism, pulmonary hypertension, renal vein thrombosis, retinal vein thrombosis, intermittent claudication, and gangrene [5]. Psychosis is a rare manifestation of APS and the pathogenesis of this neuropsychiatric manifestation remains unclear [6]. It has been listed as one of the diagnostic criteria for SLE according to the American College of Rheumatology (ACR) guidelines [7]. In a similar context, it has also been classified as a psychotic disorder due to general medical conditions in the Diagnostic and Statistical Manual (DSM)-5 [8]. It can present with delusions, hallucinations, disorganized behaviors, disorganized thoughts, and negative symptoms [8]. However, these symptoms should not be attributed to a psychiatric disorder unless somatic causes such as APS and SLE have been thoroughly investigated and ruled out.

In this review, we aim to systematically review case reports and case series that report the association between psychosis and APS. This review summarizes the characteristics of patients, their clinical presentation, radiological and laboratory findings, and reports their clinical outcomes.

## 2. Methods

This systematic review follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Supplementary Table 1) [9]. We developed the protocol in June 2016, which was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in July 2016 (CRD42016042979).

### 2.1. Eligibility criteria

This review identified case reports of psychotic symptoms in patients with either diagnosed or suspected APS. For this review, psychosis was defined as one of the following symptoms: delusions, hallucinations, disorganized behaviors like catatonia, and disorganized thoughts. These symptoms can occur in patients with schizophrenia and in some patients with unipolar or bipolar affective disorders when psychotic features are present. Negative symptoms (e.g., apathy and amotivation, which are included as criteria for schizophrenia) can also be present in non-psychotic illnesses such as depression. However, we included negative symptoms at the initial screening stage, no additional relevant articles were added. We, therefore, decided to exclude it from our definition of psychosis.

Only case reports were considered, so we describe the different aspects of patient care including the demographic characteristics, management, and the follow-up assessments in detail.

The inclusion criterion was: (i) clinical studies reporting psychotic symptoms in patients with APS. The exclusion criteria were: (i) studies on psychotic patients without APS; (ii) psychosis could not be explained by an underlying condition other than APS; (iii) *in vitro* or animal studies; (iv) studies with unreliable data which included non-peer reviewed publications and studies with unclear diagnoses; (v) studies with overlapped data; (vi) abstract-only articles, conference papers, review articles, theses, posters, book chapters, editorials, letters, commentaries, original articles without a detailed description of the case, and case reports with an unclear association between APS and psychosis. No restrictions on language, country, publication year, age, gender, or ethnicity of patients were applied.

### 2.2. Search strategy

In June 2016, eight electronic databases were systematically searched for relevant publications, including PubMed, Scopus, Web of Science, Google Scholar, PsychINFO, WHO Global Health Library (GHL), POPLINE, and the APA database using the following search terms: (antiphospholipid OR antiphospholipids) AND (psychosis OR

psychoses OR psychotic). For Google Scholar, the following search strategy was used: (“antiphospholipid” AND at least one of the following: “psychosis OR psychoses OR psychotic”), with the search restricted to “title”. The manual search of references and relevant articles for included studies was performed by two independent reviewers.

### 2.3. Study selection

Search results from the eight databases were imported to Endnote × 7 (Thompson Reuter, CA, USA) to remove any duplicates. Three independent reviewers performed title and abstract screening (when available) followed by the full-text screening of the included articles by using the predetermined eligibility criteria. In the case of disagreement, the consensus was reached by discussion among reviewers or guidance from a senior reviewer (AH).

### 2.4. Data extraction

Data were extracted independently by three reviewers and was cross-checked for accuracy by a fourth independent reviewer. In the case of disagreement, the consensus was reached by discussion among reviewers or guidance from a senior reviewer (AH).

Considering the goal of this study, a standardized template was developed after a pilot extraction of the three most relevant articles. The extracted data included: authors, journal, year of publication, language, country of authors, admitting departments, age, gender, past medical history, psychotic symptoms, other psychiatric and neurological manifestations, immunological status, underlying etiology in the case of secondary APS, radiological and neurological findings, medical treatment, duration of follow-up, and clinical outcome.

Non-English articles were translated into English by the native speakers with experience in medical translation.

### 2.5. Risk of bias assessment

The methodological quality of the included articles was independently assessed by three reviewers using the tool suggested by the Cancer Council Australia (CCA) for case-series. The disagreements in scoring were resolved by discussion and consensus. The CCA tool assessed the following three domains: subject selection, measurements of outcome, and completeness of follow-up. The results of the quality assessment are provided in numerical scores. Since this tool is not used for case-reports, it was adapted to address factors relevant to our topic. The scoring details of each domain are mentioned in Table 1.

## 3. Results

### 3.1. Study selection and characteristics

Of 454 articles, only 23 met the inclusion criteria for this review. The authors excluded 64 articles (at the title and abstract screening stage) and 10 articles (at the full-text screening stage) which were irrelevant to psychosis or APS. Two animal studies were excluded at the title and abstract screening stage while none were excluded at the full-text screening stage. Additionally, 15 articles were excluded at the title and abstract screening stage and two articles at full-text screening stage for being duplicated articles. The authors were unable to find the full-text for seven articles. In this review, 87 articles were excluded for being reviews, thesis, cohort studies, irrelevant case series, books, conferences, editorials, letters and commentaries, and original studies at the title and abstract screening stage and 35 at full-text screening stage. Supplementary Fig. 1 reflects the flow process [9].

Of the 23 included articles, 21 were case reports and two were case series. However, we included only one relevant case from each case series. All articles were published from 1995 to 2016 from various countries and continents. Eighteen articles were in English, and the

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