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Review

Cognitive disorders and antiphospholipid antibodies☆

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ABSTRACT

Cognitive disorders have frequently been described in the field of antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE). Nevertheless, the relationship between those disorders and antiphospholipid antibodies (aPL) remains unclear and seems to involve various mechanisms. Overlap with systemic lupus erythematosus, the small sample size of studies, and discrepancies in antiphospholipid antibodies and cognitive impairment determinations complicate analyses of the literature data. In this paper, we summarize current knowledge on epidemiologic, clinical data, imaging findings and treatment of cognitive dysfunction associated with aPL. We separately analyzed data on aPL-positive carriers without history of clinical feature of APS, APS patients without overlaps autoimmune disease, and SLE-associated aPL patients.

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1. Introduction

Since the early 1980s, antiphospholipid antibodies (aPL), such as anticardiolipin antibody (aCL) and lupus anticoagulant (LA), have been found to be associated with thrombosis, first in lupus patients and then independently of any systemic lupus erythematosus (SLE). Later, a third type of aPL, anti-beta2 glycoprotein I antibodies (ab2GPI), was reported. Antiphospholipid syndrome (APS) is defined by the presence of at least one aPL positivity associated with a thrombotic event or pregnancy morbidity. However, aPL were not systematically associated with an increased risk of thrombosis, especially if detected at low titers, as suggested by the prevalence of aPL in the general population, which reached 1%–5% of the population. Those results highlighted the heterogeneity of aPL and the need for a biological definition. According to current guidelines, aPL might be considered positive if aCL or ab2GPI IgG and/or IgM ≥ 40 IU/mL and/or in the presence of LA [1]. The lack of standardization and the change over time in methods of aPL measurement and threshold of positivity make it difficult to compare studies.

Neurologic involvement is one of the major features related to antiphospholipid syndrome (APS). Nevertheless, the diagnosis and treatment of neurologic manifestations commonly described in APS, such as stroke, seizures, chorea, migraines, mood disorders, and cognitive disorders remains unclear [2]. Among those manifestations, cognitive dysfunction has been consistently reported in both systemic lupus erythematosus (SLE) and in APS patients. An increased frequency of aPL has also been found in the elderly, a situation where cognitive decline and dementia are more frequent. Cognitive dysfunction is considered one of the 19 neuropsychiatric (NP) syndromes defined by the American College of Rheumatology (ACR) in patients with SLE (NPSLE) [3]. To date, there is no developed nomenclature for NP activity and diagnosis in APS [4]. Based on the ACR SLE NP nomenclature, only stroke and transient ischemic attack (TIA) have been strongly associated with elevated antiphospholipid antibodies (aPL) and are included in the definition. Secondary APS (SAPS) is a term that has been used to describe patients with overlapping syndromes, most commonly described in SLE patients. In these complex situations, confounding factors interfere with the precise determination of mechanisms involved. The lack of standardized test approaches and definition of cognitive impairment adds to the limitations in comparing studies and summarizing findings in the literature. Although the mechanisms of cognitive dysfunction found in an aPL-positive population might be explained by a prothrombotic effect (and subsequent induced infarction), data from animal experimentation suggested that inflammatory and immune effects are also involved.

Currently, the etiology and frequency of cognitive impairment in APS and the link with aPL activity remains unclear. In this review article, we summarize literature data on the relationship between cognition disorders and aPL, APS alone, or associated with SLE. Other autoimmune diseases have not been reported because of the lack of data available in other overlapping syndromes.

2. Cognitive dysfunction in aPL carriers

2.1. Epidemiology

In aPL-positive patients, the frequency of cognitive impairment ranges between 19% and 40% [5–7]. An association between aCL titers and cognitive impairment was prospectively found in 233 normal elderly subjects, despite the lack of abnormal lesions on MRI [8]. In non-elderly asymptomatic adults with elevated aPL, the frequency of cognitive impairment was 33% compared to 4% in age- and education-matched controls [5]. Arvanitakis et al. also reported an association between the presence of aPL and brain infarction, and reported cognitive and motor decline in a large cohort of 800 subjects [9]. Cognitive functions impaired in those studies were related to memory and visuomotor abilities, executive functioning, verbal learning and memory, and visuospatial ability. In contrast, gross attentional processes and fine motor skills appeared unaffected in Jacobson et al.'s study [5] (Table 1).

Relatively few studies have investigated the prevalence of dementia in aPL-positive patients. Frequency of dementia was estimated around 0%–6% in aPL carriers [10,11]. Two studies reported an association between aPL and dementia, with a significantly higher frequency of aPL reported in demented patients compared to controls [10,11] (Table 1).

2.2. Clinic

A wide range of cognitive functions is impaired in aPL-positive patients. Variability of cognitive impairment measurement, which highly depends on the specific tests administered as well as the range of domains (i.e. attention, memory, language) used to explore cognitive functioning limit the comparability of results. In addition, there are multiple ways to define “cognitive impairment” and these vary across studies. Other problems include the heterogeneity of the studied population, with subject selection—including or excluding various prior neurological or medical disorders. These limitations make it difficult to compare studies.

According to available data in the literature, the highest frequency of impairment occurred in executive functioning, attention and working memory, visual and verbal learning and memory, verbal fluency, visuospatial ability, and visuomotor speed and flexibility [5,7,12]. No demographic or clinical characteristics have been significantly associated with cognitive impairment in aPL asymptomatic carriers to date [7]. Surprisingly, in one study, the etiology of dementia was not a vascular but a degenerative process in aPL-positive patients [11], a finding that emphasizes the complex mechanisms involved.

2.3. Imaging

Neuroimaging findings in asymptomatic aPL carriers have been poorly investigated. Controversial results have been found in a prospective cohort of asymptomatic subjects, in whom frequency and extent of focal and diffuse brain abnormalities were unrelated to aCL levels [8]. However, in this study, aPL determination did not fulfill current guidelines for aPL laboratory criteria, which limited the interpretation of those results. In a recent pilot study, white matter abnormalities were common in aPL-positive patients [13]. In addition, functional MRI findings indicated abnormal brain activity in the frontal, temporal, and parietal lobes during executive function and working memory tasks [13].

2.4. Treatment

Treatment of cognition disorders in aPL carriers is not yet established and there is not enough data to raise specific therapeutic recommendations. Only one uncontrolled non-randomized clinical trial is available for review, and was designed to evaluate the effect of one immunosuppressive drug on cognitive dysfunction in 19 aPL-positive patients [14]. The aim of “RITAPS” was to evaluate the safety and benefit of rituximab in various non-criteria APS manifestations including cognitive dysfunction. Patients received 2 injections of rituximab (1 g) on days 1 and 15, and measurements of efficacy and safety were made immediately after the administration, at 24 weeks and up to 52 weeks. One strength of this study was the inclusion of cognitive assessment using 12 selected tests from a standardized neuropsychological test battery described by the ACR community [15] and shown to be reliable and valid [13]. In the six patients with cognitive dysfunction at baseline, a favorable decline in cognitive impairment was observed after treatment (3 had complete response, 1 partial, and 1 no response, 1 not analyzed). More