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Mania: Psychiatric Manifestations of the Antiphospholipid Syndrome

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Abstract

Background—Antiphospholipid syndrome (APS) is a prothrombotic condition characterized by recurrent vascular thrombosis and/or pregnancy morbidity in the presence of circulating antiphospholipid antibodies. Central nervous system (CNS) involvement is a prominent feature of APS, and many neurological manifestations have been described in published reports. There are limited data on psychiatric syndromes occurring in association with APS, and there have been no previous reports of mania associated with APS.

Method—The authors present the case of a 31-year-old man who experienced an acute manic episode in association with APS. They review the literature on psychiatric manifestations of APS, discuss potential mechanisms of CNS pathogenesis, and consider diagnostic and treatment implications of the co-occurrence of APS and psychiatric symptoms.

The antiphospholipid syndrome (APS), also known as Hughes syndrome, is an autoimmune condition characterized by recurrent arterial or venous thrombosis and/or pregnancy morbidity in the presence of persistently positive circulating antiphospholipid antibodies, (i.e., anticardiolipin antibody or lupus anticoagulant).^{1,2} Multiple organ systems may be affected, and a broad spectrum of clinical features, including neuropsychiatric pathology, has been described in patients with APS.³ APS is an acquired hypercoagulable state occurring most commonly in young-to-middle-aged adults, but it may also occur in children and elderly persons.⁴ Although the prevalence of APS is not known, the estimated prevalence of antiphospholipid antibodies (aPL) in the general population is 2%–5%.^{4,5}

CNS involvement is a prominent feature of APS, and it has been well described.^{10–14} Both thrombotic neurological events and nonthrombotic CNS symptoms are associated with APS. In a study of 1,000 patients with APS, neurological manifestations such as stroke and migraine were among the most common clinical features, occurring at a rate of about 20%.³ Other neurological syndromes, including epilepsy, cognitive dysfunction, dementia, chorea, multiple sclerosis (MS)-like syndromes, Guillain-Barre-like syndrome, and sensorineuronal hearing loss have also been reported.^{10–14}

Despite the frequency of CNS involvement in APS, there has been surprisingly little research on psychiatric features associated with this autoimmune syndrome. Psychiatric manifestations, such as psychosis, delirium, depression, anxiety, and aggressive behavior have been described in association with aPL and APS. Schwartz et al.¹⁵ studied 34 psychotropic medication-naïve, acutely psychotic patients without any known autoimmune disorders. They found an increased

prevalence of both anticardiolipin antibody (aCL) and lupus anticoagulant (LA) in these patients, as compared with healthy control subjects, suggesting that these autoantibodies are not simply the result of pharmacological treatment, as previous reports have indicated. Kurtz¹⁶ described a case in which APS may have presented with psychosis many years before the onset of somatic symptoms. Chinnery et al.¹⁷ reported a case of fulminant encephalopathy associated with catastrophic APS, a condition in which multiple vascular occlusions occur in several systems over a relatively short period of time, resulting in multi-organ failure and a high mortality rate.

Depression^{11,18–20} and aggressive behaviors¹⁴ associated with APS have also been mentioned in the literature. Maes et al.²¹ reported significantly higher titers of aPL in 63 depressed patients, as compared with healthy controls. Gorman and Cummings²² described a series of seven patients who presented with neurobehavioral findings (including irritability, mood lability, suicidal ideation, slowed thinking, akathisia, and movement disturbances) and were found to have elevated titers of aPL and/or APS. Mania has not been previously reported in association with APS or aPL.

Case Report

A 31-year-old male graduate student, “Mr. A,” presented to the outpatient psychiatry clinic at a university hospital for management of bipolar disorder; 4 months earlier, he had experienced a manic episode. At that time, his physical exam was unremarkable. Also, medical work-up revealed normal laboratory values (including CBC, chemistries, liver-function tests, thyroid-stimulating hormone, rapid plasma reagin test, vitamin B₁₂, folate, and urinalysis), negative urine toxicology screen, and normal brain MRI. Initially, he was stabilized with haloperidol and subsequently managed with lithium 1,200 mg and olanzapine 20 mg per day. Over the next several months, olanzapine was tapered to 5 mg per day because of excessive somnolence.

One year before the manic episode, Mr. A’s father had died suddenly from a stroke, and Mr. A withdrew from his graduate program for a semester. Upon his return to graduate studies, he experienced cognitive problems (e.g., poor concentration and focus), in the absence of mood symptoms. As a result of his cognitive difficulties, he withdrew from classes again. Additional history revealed episodic marijuana use since his early 20s. Family history was positive for thrombotic events (his father had had fatal cerebrovascular ischemia, and a paternal uncle died of a massive pulmonary embolism) and a history suggestive of bipolar disorder in his father.

Mr. A’s chief complaints on presentation to our outpatient clinic were problems with attention, concentration, and excessive sedation, all of which he believed were medication-induced. He was unable to organize and write research papers assigned in his graduate program. Olanzapine was discontinued in an effort to improve these symptoms, and he was maintained on lithium monotherapy. Nonetheless, his cognitive complaints persisted.

A few weeks later, and approximately 5 months after the index manic episode, Mr. A presented to the emergency room with complaints of acute chest pain and shortness of breath. CT scan of the chest showed bilateral pulmonary emboli. He was admitted to the intensive care unit, and anticoagulation therapy with warfarin and enoxaparin was begun. Further laboratory testing showed circulating LA; however, aCL was negative. A diagnosis of APS was established, with repeat laboratory testing confirming persistently positive LA, and he was maintained on warfarin therapy. He continued outpatient psychiatric care with lithium monotherapy. Aripiprazole was added later for symptoms of conceptual disorganization. The patient’s cognitive symptoms gradually improved.

Discussion

To our knowledge, this is the first report of mania described in association with APS. The precise mechanisms underlying CNS pathology in APS have not been elucidated, and it remains unclear why the brain is particularly vulnerable in patients with APS.

The two most common clinical manifestations of APS are venous thrombosis and cerebral ischemia due to arterial thrombosis.¹³ Approximately 5%–10% of patients with deep-vein thrombosis have APS.⁴ Consequently, hypercoagulability is thought to be a primary mechanism of neurological involvement. The pathophysiology of thrombosis is not fully understood, but it is known that aPL are autoantibodies directed against beta₂-glycoprotein-1 (a plasma protein) or prothrombin. These antigen–antibody complexes subsequently bind anionic phospholipids on the endothelial wall. As a result, there is an alteration in the regulation of blood coagulation, leading to a procoagulant state.^{4,5}

Various other APS-associated neurological syndromes, such as optic atrophy, headaches, cognitive dysfunction, psychosis, depression, transverse myelopathy, MS-like disease, epilepsy, and chorea often cannot be solely attributed to hypercoagulability.¹³ Moreover, some patients with neurologic symptoms including cognitive dysfunction, headaches, and chorea have no lesions on CT scan or brain MRI, suggesting that thrombosis may not be the sole mechanism.¹⁴ Studies have suggested that aPL may have more direct effects on the CNS, and animal models lend support to this possible mechanism. For example, hyperactivity and anxiety behaviors have been observed in animal models of APS and aPL, particularly after prolonged exposure to antibodies.^{14,19,20} It has been suggested that aPL-mediated binding of neurons or glial cells subsequently disrupts their functioning.^{11,13} Other studies have shown aPL to bind to mouse brain tissue and inhibit astrocyte proliferation.¹³

The role of aPL in producing neuropsychiatric syndromes has been studied in depth in patients with another autoimmune syndrome, systemic lupus erythematosus (SLE), in whom the rate of aPL ranges between 25% and 50%; aPL immunoreactivity is associated with both the clinical features of neuropsychiatric systemic lupus erythematosus (NPSLE) and with brain MRI abnormalities, such as white-matter hyperintensities, in these patients.^{25,26} The findings suggest that certain antigens in the brain, including phospholipids, could become the target of autoantibody-mediated neuronal dysfunction or cytotoxicity and thus produce clinical neuropsychiatric symptoms in patients with SLE. However, not all studies of SLE are consistent with this hypothesis; some investigators have not found a significant association between aPL and abnormal brain MRI, SPECT, or PET scans.²⁷

As mentioned earlier, aPL may be present in healthy individuals. The prevalence of aPL in healthy children may be as high as 11%–28%. Immunizations and viral and bacterial infections have been postulated to give rise to these naturally-occurring autoantibodies.^{6,7} Furthermore, studies of healthy elderly subjects suggest that aPL titers may increase with age.⁵ Also, although aPL can be present in both medicated and unmedicated patients, several pharmacologic therapies, including the neuroleptic chlorpromazine, have been associated with aCL and LA.^{8,9} However, aPL resulting from medication exposure are typically not associated with thrombotic events/fetal loss and are usually of the IgM isotype, as opposed to the IgG isotype.⁴

Whereas no causal role for aPL in producing neuropsychiatric symptoms can be demonstrated from this case, the patient's father also has a history of manic-like behaviors and thrombosis, which supports the hypothesis that psychiatric syndromes may occur in conjunction with APS. It is known that relatives of patients with APS are more likely to show aPL and APS.

Anecdotal reports have described improvement in APS-associated symptoms such as migraines, dementia, or cognitive dysfunction in response to anticoagulants alone.²⁸ Similar effects of anticoagulant therapy on psychiatric symptoms in patients with APS are possible but have not been described. It is difficult to ascertain the exact role of anticoagulant therapy on the psychiatric symptoms of the patient presented here. Psychiatric symptoms due to organic etiologies such as stroke, thyroid dysfunction, and SLE often improve once the underlying disease process has been treated. Whether this is true in APS remains unknown.^{29,30}

Although the presence of aPL may be a risk factor for the development of psychiatric symptoms, there were other potential risk factors in our patient. For example, he experienced significant psychosocial stress, including the death of his father and academic stress in the year preceding both his medical and psychiatric diagnoses. It is known that psychosocial stressors often act as environmental triggers for mood episodes in bipolar illness. Also, the psychosocial burden of the disease may have contributed to the development of psychiatric symptoms.

Conclusion

A wide variety of neuropsychiatric symptoms have been described in association with APS. This case of a first episode of mania in the context of APS suggests the possibility of aPL effects in the CNS, perhaps due to thrombosis or direct effects via immune mechanisms.

Neuropsychiatric features of APS can manifest years before systemic involvement and should be considered in the evaluation of the psychiatric patient. The utility and feasibility of routine antibody screening for patients presenting with psychiatric symptoms and personal and/or family history of thrombotic events or pregnancy morbidity is unclear and is a subject for further study. Given that aPL may be transiently elevated in the general population or medication-induced, cautious interpretation of patients' results is warranted, and the presence of these antibodies may not fully explain a given patient's neuropsychiatric symptoms. Current recommendations for aPL testing are for 1) patients with known autoimmune disease and neuropsychiatric manifestations; 2) individuals without known autoimmune disease (especially those under the age of 40) who develop ischemic cerebral events; 3) patients with "nonclassic" presentations of neurological conditions such as MS or atypical seizures; and; 4) patients (especially under the age of 40) with multiple hyperintensity lesions on brain MRI, with no other known etiology.¹³

More research is needed to understand the pathophysiology of aPL-induced CNS pathology and resultant neuropsychiatric syndromes. The possible role of anticoagulants alone for the treatment of psychiatric symptoms is controversial and has not been examined, but might be an area for further study. In the meantime, the mainstay of managing psychiatric disorders in patients with APS should be to use standard psychiatric therapies for symptom management on the basis of current empirical evidence.

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