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A Patient With Bipolar Disorder and Antiphospholipid Syndrome

Jimmy N. Avari, MD¹ and Robert C. Young, MD¹

¹Department of Psychiatry, Weill Medical College of Cornell University, New York Presbyterian Hospital, New York, NY, USA

Abstract

Antiphospholipidsyndrome (APS) is an autoimmune disorder which causes a hyper-coagulable state characterized by recurrent thrombosis. It has a diverse range of central nervous system manifestations. We describe a case of a 61 year old man with bipolar disorder and APS, and we compare this to a previously reported case. Additionally, we reviewed literature regarding APS-related markers and the relationship of APS to other psychiatric and neurologic illnesses. We discuss possible mechanisms for an association between APS and bipolar disorder. We encourage clinicians to be aware of this possible relationship and have proposed research strategies.

Keywords

bipolar disorder; antiphospholipid syndrome; central nervous system

Introduction

Antiphospholipid syndrome (APS) or Hughes syndrome is an autoimmune disorder. The current diagnostic criteria are at least one clinical criterion (vascular thrombosis or pregnancy morbidity) together with at least one laboratory criterion (lupus anticoagulant, anticardiolipin [aCL] antibody of immunoglobulin [Ig] G/IgM isotype, anti- β 2-glycoprotein-1 antibody of IgG/IgM isotype).¹ The recurrent venous and/or arterial thrombosis that is commonly associated with APS reflects hypercoagulability that can affect many organ systems.

Central nervous system (CNS) manifestations of APS reportedly include epilepsy, cognitive dysfunction, depression, dementia, and chorea.² The psychiatric and behavioral disorders in patients with APS have been described either with or without arterial and venous thrombotic events. We describe a patient with bipolar disorder and APS.

Case

Mr A, a 61-year-old caucasian male, was admitted to a university-based inpatient psychiatric unit after traveling 900 miles in search of “adequate psychiatric care.” He had recently been psychiatrically hospitalized elsewhere, but he had signed out against medical advice. On presentation to the emergency room, he was elated and grandiose, with loud, pressured speech, and psychomotor agitation.

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Corresponding Author: Jimmy N. Avari, Department of Psychiatry, Weill Medical College of Cornell University, New York Presbyterian Hospital, 21 Bloomingdale Rd, White Plains, NY 10605, USA, jia9010@med.cornell.edu.

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Mr A reported the onset of mood disorder at about age 30, initially presenting as a depressive episode. Manic episodes subsequently predominated, beginning at age 40 when he was diagnosed with bipolar disorder. He was psychiatrically hospitalized twice after being noncompliant with medications. He reported a history of trials of lithium, valproate, and quetiapine but reported that the most effective medications were lamotrigine and olanzapine.

His medical history was significant for hypercholesterolemia, degenerative joint disease, and two occurrences of deep vein thrombosis, the first of which was 6 years prior to this admission. Levels of aCL IgG were high on two occasions, immediately after his first thrombosis and 2 years later. He was diagnosed with APS and subsequently treated with warfarin. He denied ever previously being warned that he was at increased risk of thrombosis. He had multiple medical hospitalizations associated with emergency room visits. Computed tomography of the head at both 2 years and 1 year prior to this admission was unremarkable.

On the current admission, his blood chemistries, hematology, and thyroid stimulating hormone were within normal limits. His neurological examination was unremarkable. He scored a 30 (range 0–60) on the Young Mania Rating Scale and 28 (range 0–30) on the Folstein Mini Mental State Examination.

Mr A was treated with lamotrigine up to 200 mg/d, because he refused classical mood stabilizers, and olanzapine 15 mg/d. He showed an improvement in his manic symptoms over 2 weeks and had no complaints of side effects. He achieved an international normalized ratio of 3.1, taking a daily dose of 15 mg of warfarin.

Discussion

To our knowledge, this is the second case of mania reported in a patient with APS. Raza et al³ previously reported a 31-year-old man who presented with a manic episode in the context of a normal medical workup and brain magnetic resonance imaging (MRI). He had a paternal family history of both thrombotic events and bipolar disorder. His manic symptoms preceded the first evidence of pulmonary thrombosis by 5 months and he responded to a combination of lithium and aripiprazole.

Mr A is similar to that case in gender and in having a history of psychiatric symptoms preceding the onset of peripheral thrombosis and diagnosis of APS. Mr A had a history of depressive as well as manic episodes, and Raza et al described a patient who had withdrawn from school, had impaired attention and concentration, and complained of fatigue, both before and after a manic episode. Both cases lacked focal neurological findings and structural neuroimaging abnormality.

These cases have different intervals between the onset of the first manic and depressive episodes and the diagnosis of APS. Raza's patient presented with a manic episode 5 months before being diagnosed with APS; in our case, it was about 15 years prior. Additionally, Raza's case had a one year interval between depression and manifestation of APS, whereas Mr A had a 25 year interval. These and other aspects of the two cases are summarized in Table 1. The age at onset of the abnormal immunological tests in these cases is not known.

The characteristic laboratory finding of APS is persistently elevated levels of antiphospholipid antibodies (aPL), for example, aCL and antiphosphatidylserine antibodies.² The levels of aCL IgG appear to be most closely related to thrombotic events.⁴

The prevalence of APS is estimated to be between 2% and 5% in the general population, with no known racial predominance. It is commonly diagnosed in young-to-middle-aged women. Multiple comorbid conditions are described, the most common being systemic lupus erythematosus. APS is also associated with other autoimmune disorders.

The APS-related immune markers are associated with other psychiatric diagnoses and symptoms, including vascular and degenerative forms of dementia, psychotic disorders, and depression.² Mosek et al⁵ observed that 5 of 87 demented patients and none of the 69 controls had significantly elevated aCL IgG; 4 of these 5 patients had a clinical diagnosis of Alzheimer dementia. Gorman and Cummings⁶ described 7 patients that presented with behavioral disturbance and had at least moderate levels of aCL; 3 of the 7 were diagnosed with vascular dementia and 4 had features including mood lability, paranoid delusions, visual distortions, and dissociative symptoms. Five had abnormal MRI findings, one had equivocal right parietal cortical changes, and one had a normal study. Schwartz et al⁷ found elevated levels of aCL IgG in 8 of 34 unmedicated patients admitted with acute psychosis. Depression has also been a proposed manifestation of APS.²

Our experience with Mr A, taken together with the report by Raza,³ suggests a possible association between APS and bipolar disorder, but there are several limitations that must be considered. The first of these is inherent in the case report method; the co-occurrence noted may be coincidental. Second, aPL IgG can be elevated by the use of medications, including neuroleptics, and Mr A did have a history of intermittent treatment with neuroleptics; however, he was often noncompliant with medications, and in cases where aCL is elevated by medications, it is usually the IgM isotype and not IgG—the latter being the case in our patient.⁸ Finally, in Mr A, computed tomography rather than MRI results were available.

While most literature attributes neuropsychiatric abnormalities in APS to vascular occlusion, both chorea and partial seizures have been reported to occur without vascular occlusion.^{9,10} If an association between APS or APS-related markers and bipolar disorder was demonstrated by focused studies, the direction of the relationship would need to be clarified, and both vascular and direct mechanisms could be considered.

Bipolar disorders are a heterogeneous group of illnesses; among these, there is evidence for a vascular component to pathophysiology, particularly in relatively late-onset cases such as Mr A.^{11,12} The risk factors for “vascular mania” are systemic disorders that increase the probability of developing cerebrovascular disease.¹³ The APS-related immunological abnormalities can contribute to cerebrovascular disease, and therefore they may be explored as possible risk factors for bipolar disorders.

Direct effects of aPLs are another group of mechanisms for a possible causal association between APS-related markers and bipolar disorder. Chapman and Shoenfeld¹⁴ observed that mice immunized with β 2-glycoprotein 1, an autoantigen in APS, developed hyperactivity and anxiety behavior after 4 months of having elevated levels of aPL IgG; hyperactivity and anxiety are the clinical features that can be associated with bipolar disorder. Also, Chapman et al¹⁵ demonstrated that aPLs directly depolarized purified rat brain stem synaptoneurosome. Khamashta⁸ hypothesized that aPLs directly cause damage in the basal ganglia and that this is part of the pathophysiology of chorea associated with APS; subcortical pathophysiology has been implicated in bipolar disorder. Also, elevated antiphosphatidylinositol antibodies are another serological marker of APS¹⁶; it has been suggested that antibodies interfere with intracellular signal transduction.¹⁷

Another direction for a relationship between bipolar disorder or other psychiatric disorder and APS or APS-related markers could also be considered. Preexisting mood disorder might aggravate such an autoimmune process.

We encourage clinicians to be aware of the possible relationships between APS and bipolar disorder and to report cases where these occur in the same patient. In addition, research strategies might include assessment of mood disorder symptoms in a group of individuals with APS and testing for APS-related markers in patients with bipolar disorders and comparison groups.

Conclusion

We have described a patient with bipolar disorder and APS and compared it to a case previously reported. We also have reviewed other CNS disorders that have occurred in association with APS-related autoimmune markers. We have indicated some mechanisms for possible relationships between these APS and bipolar disorder.

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Table 1

Comparison of Mr A and Raza Case Report

	Mr A	Raza et al
Age	61 years	31 years
Gender	M	M
Presence of psychosis in manic episode	No	No
Family history of APS or mood disorder	None	Father—thrombosis, bipolar disorder Paternal uncle—thrombosis
Neuroimaging findings	None (CT)	None (MRI)
Age at diagnosis of APS	About 55 years	31 years
Age at onset of first depressive episode	About 30 years	30 years
Age at onset of bipolar disorder (first manic episode)	About 40 years	30 to 31 years

Abbreviations: APS, antiphospholipid syndrome; MRI, magnetic resonance imaging; CT, computed tomography.