KANSAS JOURNAL of MEDICINE

CASE REPORT

Antiphospholipid Antibody Syndrome Causing Progressive Central Nervous System Dysfunction in a Young Patient

Lindsey L. Bupp, M.S.[1,2], Ryan W. Schroeder, Psy.D.[1]
[1]University of Kansas School of Medicine-Wichita
Department of Psychiatry and Behavioral Sciences
[2]Wichita State University, Wichita, KS
Department of Psychology

INTRODUCTION

Antiphospholipid antibody syndrome (APS), also known as Hughes Syndrome, is an autoimmune disorder characterized by the presence of antiphospholipid antibodies (aPLs) and a hypercoagulability of blood which results in thrombotic events.[1] Diagnosis of definite APS, per the standards set forth by the International Congress on Antiphospholipid Antibodies, requires both clinical and laboratory corroboration.[2] Clinically, patients must present with one or more episodes of arterial, venous, or small vessel thrombosis and/or an adverse obstetric event such as spontaneous abortion. Laboratory findings must confirm elevated levels of any one of the following aPLs: lupus anticoagulant (LA), anticardiolipin antibody (aCL), or anti-β_2 glycoprotein-1 antibody.[2] This disorder can occur in association with systemic lupus erythematosus (SLE) or another rheumatic or autoimmune disease, however, approximately half of patients with APS show no evidence of a definable associated disease.[3] In the past, these two manifestations of the disorder have been referred to as secondary and primary APS, respectively, but the current preferred terminology is APS with or without associated rheumatic disease.[2]

The exact cause of APS and recurrent thrombosis is not clear, as the presence of aPLs alone is not sufficient for a diagnosis, with 1 - 5% of healthy individuals testing positive for aPL antibodies.[4] Furthermore, the clinical manifestation of APS tends to be heterogeneous as hypercoagulability and thrombosis can affect any organ system in the body. However, involvement of cerebral large vessels is frequent and, after venous thrombosis, the most common clinical symptoms of this disease tend to be transient ischemic attacks (TIAs) and stroke.[5] Other neurological manifestations can include chorea, epilepsy, multiple sclerosis like lesions, psychiatric disorders such as depression and psychosis, migraine, and cognitive impairment.[6]

Cognitive abnormalities have been documented in individuals with elevated aPLs as well as APS.[7,8] Between 2 - 5% of patients with APS develop dementia or major neurocognitive impairment, while approximately 35% display mild to moderate cognitive impairment.[9,10] The most common cognitive difficulties tend to be in the domains of attention, verbal fluency, verbal learning, executive functioning, and short term memory.[11,12] Imaging of the brain, when available, often indicates diffuse and focal ischemic changes, cortical infarcts, and/or cerebral atrophy.[6,13]

The present case study outlines a woman with APS who developed psychiatric and motor-related issues, as well as progressive cognitive impairment, at a relatively young age. She underwent a neuropsychological evaluation in 2013 at the request of her neurologist.

CASE REPORT

The patient was a 41-year-old, right-handed, multi-racial female. Her educational history was significant for completing high school and trade school. She was employed until 2010 when she became disabled due to chronic fatigue and anxiety. At the time of the neuropsychological evaluation, she was living with her second husband of 2 ½ years.

The patient's medical history was significant for APS (diagnosed in 1998), chronic fatigue syndrome, multiple prior head injuries without loss of consciousness (secondary to physical abuse from her first husband) during the late 1990s to early 2000s, and a head injury with skull fracture and loss of consciousness (LOC; of approximately 24 hours according to records) secondary to a motor vehicle accident in 1989. The patient's psychiatric history was significant for depression and psychosis, which reportedly began in 2005. Because of her psychosis, she was psychiatrically hospitalized three times, with the most recent time being in 2012. She carried the following psychiatric diagnoses: Mood Disorder Not Otherwise Specified, Psychotic Disorder Not Otherwise Specified, and Dependent Personality Disorder. Her mood and psychotic disorders were thought to be the result of her APS. Family history was significant for a myocardial infarct in the patient's mother. The patient's medications at the time of the neuropsychological evaluation included paroxetine hydrochloride 20 mg, sulfamethoxazole and trimethoprim DS 800 - 160 mg twice daily, benztropine mesylate 1 mg, lamotrigine 50 mg, asenapine 10 mg, and acyclovir 200 mg as needed.

CLINICAL COURSE OF APS

The patient was diagnosed with APS at the age of 27 after her second miscarriage. Since that time, the patient has had multiple transient ischemic attacks secondary to this syndrome, the most recent of which occurred one month prior to the neuropsychological evaluation. Over the past eight years, the patient has had depression associated with psychosis, while over the past three years she has had worsening depression and a progressive decline in her motor and cognitive abilities. An MRI of the brain was conducted just prior to the neuropsychological evaluation

secondary to the patient's decline in functioning, and medical records indicated that the results showed "significant" cortical atrophy along with subcortical white matter changes (Figure 1). This reflected a recent change, as prior neuroimaging studies (CT from 2010 and MRI from 2008) did not reveal cortical atrophy and only showed chronic periventricular white matter disease. The patient also underwent a lupus work up, which revealed that her antinuclear antibody was positive at 1:640.

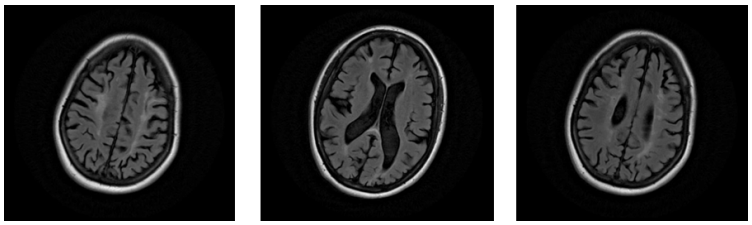

Figure 1. MRI of the brain showed "significant" cortical atrophy along with subcortical white matter changes.

CLINICAL PRESENTATION

As a result of the patient's progressive decline in functioning, she was referred for a neuropsychological evaluation. At the clinical interview, the patient's motor problems were reported to have caused reduced mobility in the patient's limbs and eye movements (the latter resulting in visual scanning difficulties). The patient and her husband indicated that she frequently stumbled and fell when walking, and her gait appeared to be unsteady. She reported her cognitive difficulties to be widespread, but short-term memory seemed to be the most affected, as she would forget what she was doing mid-task. An example provided by the patient's husband was that the patient once turned water on to do dishes, turned around to get things organized, forgot that she was going to do the dishes, and walked away with the water running. He also reported that the patient would forget to take her medications and that she stopped driving due to concerns about her ability to do so safely.

During the course of the evaluation, the patient demonstrated difficulty recalling details of her background and medical history including when her symptoms began. While she was able to comprehend casual interview questions, she required repetition and elaboration of formal test instructions to comprehend them. Her speech was slow in rate, somewhat soft in volume, and occasionally mildly disarticulate. Thought processes were slow but generally logical and coherent. However, perseveration was noted at times during the testing session. There was no evidence of delusions or hallucinations, but the patient noted that she recently had been experiencing some degree of paranoia. Affect was somewhat dysphoric. Mood was described as fluctuating based on the weather. Psychomotor retardation was evident. Insight into her cognitive functioning was impaired.

Neuropsychological testing was valid based on the patient's performance on empirically-derived validity tests. Premorbid intellectual abilities were estimated objectively to be in the average range of functioning (estimated IQ = 102; 55th percentile). This was calculated by entering the patient's demographic variables (i.e., age, sex, ethnicity, and level of education) and performance on a word reading task into an established predictive equation.[14] To measure the patient's current intellectual functioning, she was administered the Wechsler Abbreviated Scale of Intelligence - Second Edition, which yielded an Intelligence Quotient of 69 (2nd percentile), a significant decline in intellectual functioning of two standard deviations and a change from "average" to "deficient."

The Repeatable Battery for the Assessment of Neuropsychological Status was administered to examine a range of current neurocognitive functions. This measure is composed of 12 subtests that assess verbal and visual learning and memory, visuospatial abilities, expressive language abilities, mental processing speed, and simple attention span. The patient's performance was moderately to severely impaired (< 1st percentile) on all subtests with the exception of two: a measure of visuospatial line orientation (mildly impaired, 7th percentile) and a measure of confrontation naming (average, 30th percentile). The Brief Visuospatial Memory Test - Revised was administered as an assessment of visuospatial learning and memory. Again, the patient's performance was moderately to severely impaired (< 1st percentile).

The Delis-Kaplan Executive Functioning System was administered as a measure of higher-level cognition including sustained attention, set-shifting, inhibition, and mental flexibility. Across these tasks the patient's performance was moderately to severely impaired (< 1st percentile). Measures of finger tapping, grip strength, and grooved pegboard also were administered to assess the patient's motor control and manual dexterity. Finger tapping and grooved pegboard had to be discontinued due to psychomotor retardation, spasticity, and poor coordination, particularly with the non-dominant (left) hand. Grip strength was bilaterally impaired but the non-dominant (left) hand was significantly weaker than the dominant (right) hand. Finally, brief depression and anxiety screening tests indicated that the patient was experiencing moderate levels of both conditions.

DISCUSSION

The incidence of dementia or major neurocognitive disorder secondary to APS is rare in the literature, with only a small percentage of patients subsequently developing severe cognitive problems.[9,10] In the current case, comprehensive neuropsychological data were presented on a relatively young patient with APS who was thought to have developed major neurocognitive impairment, in addition to psychiatric and motor-related symptomology, due to her APS. Neuropsychological testing showed essentially global cerebral impairment, resulting in significant deficits in intellectual functioning, attention, mental processing speed, verbal fluency, visuospatial ability, learning and memory, executive functioning, and bilateral motor functioning. When compared to neurologically healthy age-matched individuals, this patient's scores were consistently at or below the 1st percentile. The only test score that was

not within an impaired range of functioning was a score from a confrontation naming test. However, this test has been criticized as it has been shown to have minimal sensitivity to cognitive dysfunction even in patients with neurodegenerative dementia processes.[15-17] Overall, it was concluded that neuropsychological testing provided strong evidence of a significant and essentially global central nervous system abnormality.

Because the patient has a history of head trauma, the possibility that her symptoms might have resulted from this head trauma, instead of APS, should be addressed. The patient's history of head trauma was not a primary contributor for numerous reasons. The patient's head injury with skull fracture occurred in 1989, her other head injuries (due to physical abuse) occurred in the late 1990s to early 2000s, and no additional head injuries occurred after that date. These head injuries were not thought to have resulted in any significant, longstanding cognitive difficulties, as the patient continued to work successfully as a hairdresser until 2010. Neither she nor her husband reported any significant cognitive difficulties until 2010. Furthermore, an MRI of the brain from 2008 and a CT of the head in 2010 showed no cortical atrophy and only mild chronic periventricular white matter disease. Thus, there was no evidence of any significant cognitive or neurologic dysfunction predating 2010, and there was no evidence of significant residual cognitive deficits from the prior head trauma.

In 2010, the patient began having more TIAs and her husband noticed increased cognitive, motor, and psychiatric issues. These issues progressed over time and an updated MRI of the brain, conducted in 2013, showed "significant" cortical atrophy along with subcortical white matter changes (Figure 1). Given that the onset of the patient's symptoms corresponded with an increase in TIAs (which are common in APS),[5] that updated neuroimaging showed cortical atrophy and subcortical white matter changes (which is not uncommon in APS),[6,13] that the progressing symptoms included increased cognitive, psychiatric, and motor abnormalities (all of which are common in APS),[6] and that the patient was relatively young and physically healthy outside of her APS-related symptomatology, and had no other significant risk factors for early-onset dementia, it was concluded that this patient's dementia very likely was due to the progression of her documented APS.

Due to the degree of cognitive impairment resulting from her dementia, a recommendation for supervision and assistance with daily activities, like driving a motor vehicle, was proposed. Additional recommendations included pursuing legal counsel to set up surrogate decision-making responsibilities (e.g., guardianship and conservatorship).

Unfortunately, the patient's prognosis was poor given the etiology and nature of her documented symptoms. Once dementia occurs, there are no treatments to reverse the cognitive impairments. Management of APS typically focuses on controlling other symptoms that are a consequence of the disease (e.g., psychiatric disturbances and motor symptoms).[18] For those patients who experience ongoing episodes of thrombosis, stroke, or transient ischemic attacks, the administration of anticoagulants and immunosuppressive drugs usually is recommended, although randomized controlled trials investigating the effectiveness of these drugs are limited.[19] Thus, evidence to suggest that these medications may prevent or delay the development of cognitive dysfunction is lacking.

At the time of the patient's neuropsychological evaluation, she was not taking any anticoagulant or immunosuppressive drugs, nor did she report past prescriptions of these medications. It is possible that the outcome of her case could have been different if such medications had been prescribed. There is not, however, a simple linear relationship between the development of cognitive dysfunction and a history of central nervous system complications in APS.[10] For example, in a study among patients with APS, three patients under the age of 30 developed dementia without a history of cerebrovascular accidents.[20] Other researchers also have cited examples of patients with APS who displayed chorea or mild cognitive impairment, but had no focal lesions on imaging.[21,22] Due to these findings, it has been suggested that the disease mechanism that leads to the development of cognitive impairment secondary to APS is more complex and cannot be explained solely by the occurrence of repeated cerebrovascular events. Other proposed ways through which APS can lead to cognitive dysfunction includes the role of aPL antibodies in the inhibition of astrocyte proliferation and disruption of vascular endothelium.[23,24] As a result, it is impossible to say whether this patient would have had some degree of cognitive decline if she would have been prescribed anticoagulants or immunosuppressive drugs prior to her recurrent cerebrovascular events. Nonetheless, aggressive preventative treatment should be considered in APS patients, especially when patients report having a history of cerebrovascular events and/or cognitive changes.

REFERENCES

[1] Sanna G, Bertolaccinni ML, Cuadrado MJ, Khamashta MA, Hughes GRV. Central nervous system involvement in the antiphospholipid (Hughes) syndrome. Rheumatology 2003; 42(2):200-213. PMID: 12595612.
[2] Miyakis S, Lockshin T, Atsumi D, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2005; 4(2):295-306. PMID: 16420554.
[3] Cohen D, Berger SP, Steup-Beekman GM, Bloemenkamp KW, Bajema IM. Diagnosis and management of the antiphospholipid syndrome. BMJ 2010; 340:c2541. PMID: 20472677.
[4] Biggioggero M, Meronin PL. The geoepidemiology of the antiphospholipid antibody syndrome. Autoimmun Rev 2010; 9(5):A299-A304. PMID: 19932199.
[5] Shah NM, Khamashta MA, Atsumi T, Hughes GR. Outcome of patients with anticardiolipin antibodies: A 10-year follow-up of 52 patients. Lupus 1998; 7(1):3-6. PMID: 9493141.
[6] Gomez-Puerta JA, Cervera R, Calvo LM, et al. Dementia associated with the antiphospholipid syndrome: Clinical and radiological characteristics of 30 patients. Rheumatology 2005;44(1):95-99. PMID:15367749.
[7] Schmidt R, Auer-Grumbach P, Fazekas F, Offenbacher H, Kapeller P. Anticardiolipin antibodies in normal subjects. Stroke 1995; 26(5):749-754. PMID: 7740561.

[8] Whitelaw DA, Spangenberg JJ, Rickman R, Hugo FH, Roberts M. The association between the antiphospholipid antibody and neuropsychological impairment in SLE. Lupus 1999; 8(6):444-448. PMID: 10483012.
[9] Rodrigues CE, Carvalho JF, Shoenfeld Y. Neurological manifestations of antiphospholipid syndrome. Eur J Clin Invest 2010; 40(4):350-359. PMID: 20192975.
[10] Tektonidou MG, Varsou N, Kotoulas G, Antoniou A, Moutsopoulos HM. Cognitive deficits in patients with antiphospholipid syndrome. Arch Intern Med 2006; 166(20):2278-2284. PMID: 17101948.
[11] Leritz E, Brandt J, Minor M, Reis-Jensen F, Petri M. Neuropsychological functioning and its relationship to antiphospholipid antibodies in patients with systemic lupus erythematosus. J Clin Exp Neuropsychol 2002; 24(4):527-533. PMID: 12187465.
[12] Jacobson MW, Rapport LJ, Keenan PA, Coleman RD, Tietjen GE. Neuropsychological deficits associated with antiphospholipid antibodies. J Clin Exp Neuropsychol 1999; 21(2):251-264. PMID: 10425522.
[13] Amoroso A, Del Porto F, Garzia P, Mariotti A, Assunta Addessi M, Afeltra A. Primary antiphospholipid syndrome cerebral atrophy: A rare association? Am J Med Sci 1999; 317(6):425-428. PMID: 10372845.
[14] Wechsler D. Wechsler Test of Adult Reading. San Antonio: The Psychological Corporation, 2001.
[15] Barker MD, Horner MD, Bachman DL. Embedded indices of effort in the repeatable battery for the assessment of neuropsychological status (RBANS) in a geriatric sample. Clin Neuropsychol 2010; 24(6):1064-1077. PMID: 20544558.
[16] Duff K, Humphreys Clark JD, O'Bryant SE, Mold JW, Schiffer RB, Sutker PB. Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: Sensitivity, specificity, and positive and negative predictive powers. Arch Clin Neuropsychol 2008; 23(5):603-612. PMID: 18639437.
[17] McKay C, Casey JE, Wertheimer J, Fichtenberg NL. Reliability and validity of the RBANS in a traumatic brain injured sample. Arch Clin Neuropsychol 2007; 22(1):91-98. PMID: 17141467.
[18] Espinoza LR. Antiphospholipid antibody syndrome: Treatment. Lupus 1996; 5(5):456-457. PMID: 8902781.
[19] Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: A systematic review. JAMA 2006; 295(9):1050-1057. PMID: 16507806.
[20] Erkan D, Yazici Y, Sobel R, Lockshin MD. Primary antiphospholipid syndrome: Functional outcome after 10 years. J Rheumatol 2000; 27(12):2817-2821. PMID: 11128669.
[21] Khamashta MA, Gil A, Anciones B, et al. Chorea in systemic lupus erythematosus: Association with antiphospholipid antibodies. Ann Rheum Dis 1988; 47(8):681-683. PMID: 3415367.
[22] Sastre-Garriga J, Montalban X. APS and the brain. Lupus 2003; 12(12):877-882. PMID: 14714905.
[23] Sun KH, Liu WT, Tsai CY, Liao TS, Lin WM, Yu CL. Inhibition of astrocyte proliferation and binding to brain tissue of anticardiolipin antibodies purified from lupus serum. Ann Rheum Dis 1992; 51(6):707-712. PMID: 1616350.
[24] Del Papa N, Guidali L, Sala A, et al. Endothelial cells as target for antiphospholipid antibodies. Human polyclonal and monoclonal anti-beta 2-glycoprotein I antibodies react in vitro with endothelial cells through adherent beta 2-glycoprotein I and induce endothelial activation. Arthritis Rheum 1997; 40(3):551-561. PMID: 9082944.

Keywords: antiphospholipid antibody syndrome, Hughes Syndrome, central nervous system