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Antiphospholipid Syndrome and the Brain in Pediatric and Adult Patients

E. Muscal [Assistant Professor]¹ and R.L. Brey [Professor and Chair]²

¹Division of Rheumatology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

²Department of Medicine, Division of Neurology, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Summary

The most common neurological manifestations of APS in all age-groups include stroke and transient ischemic attacks due to arterial thromboses and cerebral ischemia. Antiphospholipid antibodies may cause additional non-criteria neurological impairments through vascular, neuroinflammatory and direct neuronal effects. Anti-aggregant or anti-coagulant therapies are indicated for APS related ischemic strokes. Treatment regimens for asymptomatic antibody positive patients and those with refractory or recurrent disease remain controversial. There is scant literature on the epidemiology and therapy of neurological APS manifestations in pediatric patients. Assessments of modifiable cardiovascular and inherited thrombophilia risk factors are essential in patients with APS. There may be a role for novel neuroimaging modalities in quantifying APS related micro-structural brain damage. The clinical utility of statins, anti-malarials, ACE inhibitors and thrombin inhibitors warrant further research.

Keywords

antiphospholipid syndrome; cerebrovascular disease; anticardiolipin antibody; β 2 glycoprotein –I; lupus anticoagulant; thrombosis

Potential Mechanisms of Neurologic Dysfunction in APS

Antiphospholipid syndrome (APS) is a systemic autoimmune condition characterized by hypercoagulability, venous and/or arterial thromboses, and pregnancy morbidities. Neurologic dysfunction may be related to a host of immune-mediated vascular, inflammatory and direct neuronal effects (Table 1).

Antiphospholipid antibodies (aPLA) may activate endothelial cells, platelets and coagulation cascades and can exist in autoimmune disorders such as lupus. As in other vessels aPLA induce a proinflammatory and procoagulant state in human brain microvascular endothelial cells. Local ischemia due to micro-vessel thrombi opens the blood-brain barrier (BBB). In lupus patients aPLA-triggered leucoadhesion and complement activation appear to increase BBB permeability. An influx of peripherally produced autoantibodies and cytokines could then lead

Corresponding author: Robin L. Brey, M.D., University of Texas Health Science Center at San Antonio, Department of Neurology, 7703 Floyd Curl Drive San Antonio, TX 78229-3900, Phone: 210-567-4621, Fax: 210-567-1948, brey@uthscsa.edu.

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to neurotoxicity. aPLA binding of β_2 -glycoprotein I (β_2 GPI) may also impair normal inhibition of cerebrovascular atherogenesis. IL-6 release is postulated to damage neuronal and astrocyte cells in APS patients as it does in neuropsychiatric lupus subjects.¹ In experimental models anti- β_2 GPI bind neuronal and astrocyte membranes and reduce cellular viability. aPLA also depolarize synaptic rat brain extracts and may have similar effects in human nerve terminals.² aPLA may induce neurotoxicity in cells through overactivation of glutamate receptors or may exert CNS effects by directly reacting with brain lipids.³ There are associations between aPLA or lupus anticoagulants (LAC) and both platelet and endothelial cell-derived microparticles in ischemic brain diseases.⁴

Cerebrovascular Disease in Pediatric and Adult APS Studies

Conflicting data on associations between various types of aPLA or LAC and strokes may be due to study methodologies. Some studies included only baseline aPLA testing, did not include LAC testing, enrolled patients that would not currently meet APS classification criteria or did not assess aPLA/LAC at times of neurological events.

Case-control and prospective studies have shown robust associations between aPLA or LAC and incident ischemic strokes in young adults.^{5, 6} An extremely high Odds Ratio (OR) of 43.1 was reported for positive LAC tests and ischemic strokes in a study with a low LAC positivity rate in a control population (RATIO: Risk of Arterial Thrombosis in relation to Oral Contraceptives).⁶ Arterial thromboses most commonly occur in the cerebral circulation of APS patients and lead to ischemic stroke or transient ischemic attacks (TIA). Cerebral ischemia most often presents due to middle cerebral artery occlusion but may affect any cerebral arterial territory.⁷ Stroke or TIA is the initial presentation in 29.9% of adults with APS in a large European cohort.⁸ Stroke was an initial presentation in 18% of Latin American mestizo adults APS patients.⁹ Stroke/TIA events were the most frequent recurrent events in the European cohort and led to a significant proportion of the cohort deaths. Thromboses were also the leading cause of mortality in the latter five years of a prospective multi-national lupus cohort study. aPLA-associated strokes accounted for 11.8% of these events in a predominantly young female cohort.¹⁰ Cerebral manifestations (including infarcts) were also observed in 62% of the 250 patients in the European Catastrophic Antiphospholipid Antibody Syndrome (CAPS) registry.¹¹ Stroke was the cause of death in 13% of the 114 deaths in this CAPS registry.

The importance of modifiable vascular risk factors in the prevention of aPLA-associated thromboses has been shown in adult lupus research studies. In Lupus in Minorities Nature Versus Nurture (LUMINA), a large multi-ethnic US lupus cohort, the mean numbers of traditional cardiovascular risk factors were higher in patients who developed thromboses.¹² Vascular events were independently predicted by aPLA, smoking, c-reactive protein and older age. The OR of ischemic strokes in women (mean age of 39) with a positive LAC were significantly higher in smokers or users of oral contraceptives.⁶ The presence of additional prothrombotic risk factors may enhance the significance of aPLA in individual patients. Asymptomatic aPLA positive patients should be counseled about traditional cardiovascular risk factors and join smoking cessation programs. Asymptomatic women with aPLA positivity should be counseled about the additional hypercoagulable risks of oral contraception, smoking, and pregnancy.

In a few studies patients with lupus and isolated APS also show associations between valvular heart disease and CNS manifestations. LAC positivity and valvular anomalies (vegetation, thickening and regurgitation) were independent predictors of MRI proven cerebrovascular disease in lupus patients.¹³ Chronic coagulopathy and immune complex deposition may cause valvular changes and embolization to cerebral vessels. Yet, the combined presence of positive aPLA and a patent foramen ovale (PFO) or thickened left-sided heart valves did not

significantly increase subsequent cerebro-vascular events in a cohort of patients with incident strokes (The PICSS-APASS study).¹⁴ Echocardiography (preferably trans-esophageal) may be warranted in patients with stroke and APS.

The role of aPLA in pediatric strokes continues to be investigated. Transient and often non-pathogenic aPLA are more prevalent in children and often seen after infections.¹⁵ Yet, it is unclear whether primary pediatric APS is a rare entity due to less prominent childhood prothrombotic risk factors. Ischemic stroke was the initial manifestation of 26% of pediatric APS subjects in a multi-national childhood APS registry (121 subjects; both primary and secondary APS).¹⁶ Rates of stroke were higher in the primary APS subjects who were also younger at presentation. Seven percent of children in this cohort presented with cerebral sinus venous thrombosis. A small pediatric study detected increased aCL IgG antibodies in over 50% of patients with idiopathic cerebral ischemia.¹⁷ Associations between positive LAC and cerebrovascular disease were reported in a Toronto cohort study of children with lupus.¹⁸ Anti- β_2 GPI Abs were associated with cerebrovascular disease in children in an American pediatric lupus cohort.¹⁹ Only aCL IgM Abs were associated with cerebrovascular disease in another American retrospective pediatric lupus cohort study.²⁰

Non-Criteria Neurologic Events in Pediatric and Adult APS Studies

The validity of associations between aPLA and non-criteria manifestations remain controversial. Migraines (20.2%) and epilepsy (7%) are prevalent manifestations in the adult Euro-Phospholipid cohort.⁸ Chronic and recurrent small vessel ischemic events predispose patients to early-onset multi-infarct dementia.⁷ Recurrent seizures are more prevalent in lupus patients with high titer aCL antibodies and may be associated with ischemic changes. APS manifestations such as cognitive dysfunction and demyelination may have both thrombotic and non-vascular mechanisms. Prospective studies associate persistent aPLA positivity with cognitive impairments in lupus patients. Impairment is prominent in areas of attention, psychomotor speed and executive abilities and is not associated with traditional lupus autoantibodies titers.^{21, 22} aPLA mediated damage to white matter (WM) tracts and basal ganglia structures may account for multiple sclerosis-like features and movement disorders in APS patients.² WM lesions were statistically more common in adults with high-titer aCL in a study of APS patients.²³ MRI lesions were visualized in sub-cortical and juxta-cortical WM of the frontal and parietal lobes in a structure-function association study of adults with APS. The severity of these lesions predicted the number and type of cognitive domains impaired during neuropsychology evaluation.²⁴ Neuroimaging studies utilizing volumetric assessments, Magnetization Transfer Imaging (MTI), and Diffusion Weighted Imaging (DWI) reveal micro-structural changes in primary APS patients even without previous CNS events.^{25, 26} These “novel” modalities appear to differentiate APS patients from those diagnosed with Multiple Sclerosis and who have more pronounced atrophy, higher lesion load, and abnormal diffusivity.²⁵

Migraines (7%), chorea (4%) and epilepsy (3%) were the most common non-thrombotic neurologic manifestations in the only published Pediatric APS registry.¹⁶ Only the prevalence of anti- β_2 GPI Abs were found to be statistically higher in pediatric lupus patients with NPSLE in the Toronto cohort.¹⁸ aPLA (including anti- β_2 GPI) and LAC were not associated with non-thrombotic neurologic manifestations in the two pediatric lupus cohorts described above. There have been no published neuroimaging studies of pediatric APS patients. No pediatric lupus structure-function association studies to date have assessed the role of aPLA on cognition.

Current Treatment Recommendations for APS-Mediated Neurologic Manifestations: Striving for Evidence-Based Practice

Few studies have examined the efficacy of different therapies in the prevention of aPLA associated arterial ischemic strokes. The management of APS-mediated ischemic strokes are based on both retrospective and prospective studies with a predominance of venous thromboses. Two Randomized controlled trials (RCT) powered to detect the superiority of high intensity warfarin regimens challenged treatment algorithms based on higher INR targets (from retrospective studies). Neither study showed a statistically significant difference in recurrent thrombosis rates when comparing moderate vs. high intensity regimens.^{27, 28} Yet, low rates of arterial thromboses and recurrence rates in these studies call into questions their applicability to ischemic stroke.

Due to findings in the Antiphospholipid Antibodies and Stroke Study (APASS) many clinicians treat incident aPLA related cerebral arterial events with aspirin or moderate intensity warfarin (INR 2-3). An important APASS caveat is that only 14% had moderate to highly positive aCL IgG or IgM titers, only 20% had positive LAC tests, and the published analysis was based on a single positive aPLA determination. Analyses for 1770 patients receiving warfarin (INR 1.4-2.8) or aspirin (325 mg daily) were adjusted for age, sedentary lifestyle and cardiac medical history.²⁹ There were no observed increases in death or thrombotic events associated with aPLA positivity in either treatment group. Subgroup analyses for patients younger than 55 and those with cryptogenic strokes revealed similar results. There were no differences in bleeding complications between aspirin and warfarin groups.

APS experts debate the implications of these prospective trials on cerebral arterial thrombosis treatment. APASS conclusions based on single antibody measurement may not generalize to APS patients with persistent and severe disease processes. Some experts believe that the recent RCT studies did not adequately investigate therapies in aPLA-associated arterial disease. Arterial disease reflects potent antibody effects and often leads to increased morbidity and mortality. Indeed, strokes and TIAs were the most frequent recurrent thrombotic events in the Euro-Phospholipid cohort although a majority of patients were anticoagulated with an INR target of 2-3.⁸ The Euro-Phospholipid cohort investigators postulate that this warfarin regimen may only protect against venous events. Some researchers and clinicians still use high-intensity warfarin (INR 3-4) in patients with a history of lupus, recurrent thromboses or initial arterial event. Prospective studies of warfarin and aspirin in aPLA related arterial diseases are needed to settle these debates. There are no compelling data regarding treatments in the primary prevention of aPLA-associated strokes in patients without previous thrombosis. Asymptomatic, persistently aPLA-positive individuals did not benefit from low-dose aspirin for primary thrombosis prophylaxis when compared to those on placebo in a recent study.³⁰

There is no compelling evidence regarding optimal treatment of patients with recurrent thromboses while anticoagulated. A sub-therapeutic INR at time of thrombosis may represent inadequate anti-coagulation and not treatment failure. Thrombo-occlusive events despite proper INR ranges may respond to increased INR targets (> 3), or switching to heparin products (low-molecular or unfractionated) or combination therapy with aspirin. Patients with systemic inflammation during a lupus flare or those with diffuse microangiopathy (CAPS) may require intravenous immunoglobulin, plasma exchange and/or corticosteroid therapy.¹¹ There are no expert opinions or trials that have examined warfarin, aspirin or heparin performance in childhood APS. Although pediatric practices often approximate adult care only 40% of children with arterial thrombosis in the Pediatric APS registry received anticoagulation (with or without aspirin). Indeed, 5 of 8 children with recurrent arterial thromboses in this registry were not anticoagulated after their initial arterial event

Future Directions in Neuro-APS

Caring for APS patients with neurologic manifestations remains a complex endeavor that requires individualized patient risk assessment. Clinicians must recognize the limits of available evidence-based guidelines. Modifiable and genetic prothrombotic risks must be carefully assessed in all APS patients. Sub-groups of patients may require aggressive therapies and dosing regimens that may deviate from consensus statements. Patients with lupus, previous strokes, and multiple hypercoagulable risk factors require close clinical vigilance. Adult and pediatric APS researchers should guide these clinical efforts by designing studies that effectively measure treatment effects of new agents or dosing regimens. The pediatric research community must surmount the challenge of minimal APS observational data and sample size constraints.

Understanding associations between aPLA and non-stroke related neurological manifestations warrant further research support. Neuroimaging modalities that assess microstructural WM damage (such as DWI or diffusion tensor imaging), or perfusion changes (through arterial spin labeling) may allow for identification of early CNS damage in APS patients. Future APS clinical trials may also address novel vascular and immune targets. Statins are attractive agents in the treatment of APS patients as they block aPLA-induced endothelial cell activation and inhibit small GTP-binding protein mediated intracellular signaling. Downstream endothelial and platelet effects of this inhibition include: increased nitric oxide synthase and fibrinolytic activity. Statin therapy improves hyperlipidemia and may inhibit β_2 -GPI antibody induced monocyte tissue factor (TF) over-expression. ACE and adenosine uptake inhibitors may have similar effects on TF expression. Hydroxychloroquine, an anti-malarial agent long utilized in lupus, appears to have both anti-aggregant and anti-inflammatory effects. Mechanisms for this drug's action in APS include reduction of platelet activation, and modulation of B and T cell receptor signaling. Newer oral anti-coagulants, such as thrombin inhibitors may have safer profiles and require less frequent monitoring.

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Figure 1.
T2-weighted MRI of a young woman with APS and multiple ischemic strokes

Table 1

Manifestations and potential pathogenic mechanisms of aPLA in the nervous system

Neurological manifestations associated with antiphospholipid antibodies		
Stroke		
Transient ischemic attack		
Amaurosis fugax		
Transient parasthesias	Thrombotic and ischemic effects	
Cerebral venous sinus thrombosis		
Ocular ischemia		
Acute ischemic encephalopathy		
Seizures		
Cognitive impairment		
Dementia		
Optic atrophy		
Transverse myelopathy	Thrombotic, immune, neuronal effects?	
Multiple-sclerosis-like disease		
Guillian Barre syndrome		
Chorea		
Migraine		
Psychiatric disturbances		