Neurological manifestations of the antiphospholipid syndrome: risk assessments and evidence-based medicine

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SUMMARY
The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by autoantibody production and vascular thrombosis or pregnancy morbidity. Autoantibodies generated against phospholipid and phospholipid-binding proteins often impair phospholipid-dependent clotting assays (lupus anticoagulants). These autoantibodies activate endothelial cells, platelets and biochemical cascades and can exist in autoimmune disorders such as lupus. Consistently positive antibodies may worsen the severity of thrombo-occlusive disease. The most common neurological manifestations of APS include stroke and transient ischaemic attacks due to arterial thromboses. Antiphospholipid antibodies may cause additional neurological impairments through both vascular and immune mechanisms. Antiaggregant or anticoagulant therapies are indicated for APS-related ischaemic strokes. Treatment regimens for asymptomatic antibody-positive patients and those with refractory disease remain controversial. There is scant literature on neurological APS manifestations in paediatric patients. Assessment of traditional cardiovascular and inherited thrombophilia risk factors is essential in patients with APS. Modifiable risk factors and valvular heart disease may worsen thrombotic and cerebrovascular outcomes. Alternative therapies such as statins, anti-malarials, angiotensin-converting enzyme inhibitors and thrombin inhibitors warrant further research.

PREVALENCE AND AUTOIMMUNE ASSOCIATIONS
The antiphospholipid syndrome (APS) is a prevalent autoimmune disorder characterised by the persistence of procoagulant autoantibodies and clinical evidence of vascular thrombosis or pregnancy morbidity (1,2). Management of patients with APS and research of this syndrome is complicated by the diversity of its clinical manifestations and pathogenic mechanisms. The syndrome may be an isolated autoimmune phenomenon or may be found in patients with systemic lupus erythematosus (SLE) and other autoimmune disorders. It is unknown whether APS is an autoimmune coagulopathy in the spectrum of lupus (3). The clinical sequelae of isolated (primary) APS and antiphospholipid-mediated thrombosis in lupus (secondary APS) are similar. APS may account for 20% of recurrent thromboses in young adults and may be as common a thrombophilia as the factor V Leiden mutation (4). The syndrome may account for 15% of recurrent pregnancy losses. APS manifestations affect patients of both sexes and all ages (including children and the elderly). Low titre and often non-pathogenic antiphospholipid antibodies (aPL) are found in 5–10% of healthy individuals and may be transiently elevated after viral infections and drug exposures (5,6). Persistent high titre aPL antibodies are detected in less than 2% of healthy adults. aPL are found in 30% of adult and over 50% of paediatric lupus patients (6,7).

PATHOGENIC MECHANISMS: CELLULAR AND BIOCHEMICAL EVENTS
Antibodies targeting phospholipid-binding proteins such as β2-glycoprotein I (β2GPI) are central to many pathogenic APS mechanisms. These antibodies may affect endothelial cells, monocytes and platelets by mediating intracellular signalling cascades (Figure 1). Antibodies to β2GPI are generated during apoptotic clearance of cellular membranes (5). Additional antigenic targets include anionic phospholipids, prothrombin (factor II), annexin V and components of the fibrinolytic cascade (protein...
C and S) (2). aPL activate endothelial cells, monocytes and platelets and induce a prothrombotic state (8). Binding of antibodies to endothelial surfaces leads to upregulation of adhesion molecules and release of proinflammatory cytokines. aPL upregulate tissue factor (TF) expression on monocytes and endothelial cells and activate the extrinsic coagulation pathway. The antibodies potentiate platelet aggregation and enhance vasoconstriction. Complement activation is an integral component of thrombi development and fetal loss in experimental models (9,10). Complement cascade by-products further enhance platelet and endothelial damage and stimulate immune responses. Thrombotic events in APS often follow ‘second hits’ such as vascular injury/damage, infections and systemic inflammation (5).

Antiphospholipid antibodies may also have specific non-thrombogenic effects on peripheral and central nervous system tissues. Small studies have shown that anti-β2GPI bind to neuronal and astrocyte membranes in addition to the vascular endothelium (11). aPL depolarise synaptic rat brain extracts and may have similar effects in human nerve terminals (12).

**Classification criteria: clinical manifestations**

International classification criteria attempt to standardise clinical research studies and should not replace clinical decision-making and individualised assessment of thrombotic risks. The 1999 Sapporo preliminary classification criteria have high sensitivity and specificity in lupus patients. According to recent criteria revisions (Table 1), a definitive diagnosis of APS depends on at least one clinical manifestation of vascular thrombosis or pregnancy morbidity (3). Vascular manifestations include arterial, venous or small vessel thromboses that are confirmed by imaging or histopathology and are not explained by vasculitis. Recurrent thromboses tend to occur in the same vascular distribution as initial events and are most prevalent within 6 months of discontinuing anticoagulation (6). APS-associated pregnancy morbidities include: miscarriages after the 10th gestational week, placental insufficiency and premature births before 34 weeks, or multiple consecutive fetal losses before the 10th gestational week (Table 1).

Additional clinical features associated with APS include neurological manifestations unrelated to...
stroke, nephropathy, valvular heart disease, thrombocytopenia and livedo reticularis (3). These features are not included in the specific classification criteria but are important in clinical practice. Patients may also present with catastrophic APS (CAPS) characterised by a multi-organ thrombotic microangiopathy with high mortality (6).

**Classification criteria: laboratory findings**

In addition to clinical events, APS diagnosis includes positive anticardiolipin antibody (aCL), $\beta_2$GPI antibody or the presence of a lupus anticoagulant. Positive laboratory findings should be present on two or more occasions at least 12 weeks apart according to revised criteria (Table 2). Both aCL and $\beta_2$GPI tests should be performed by standardised ELISA techniques and deemed significant when medium or high titres are discovered. Lupus anticoagulant tests (LA or LAC) detect impairment of phospholipid-dependent clotting assays (intrinsic and extrinsic coagulation pathways). Prolongation of activated partial thromboplastin times often indicates lupus anticoagulant positivity in patients with APS. International standards for lupus anticoagulant testing include: prolongation of at least one phospholipid-dependent coagulation assay (most commonly the dilute Russell viper venom test), inability to correct anticoagulant effects with plasma (ruling out a factor deficiency), and correction of anticoagulant effects with excess phospholipid (13). While one positive test indicates the presence of a lupus anticoagulant, it is recommended that laboratories perform multiple tests with differing assay principles (3). A recent systemic review of APS studies showed that lupus anticoagulants had a stronger association with thromboses than aCL antibodies (odds ratio of 11 vs. 1.6) (14). In the review higher aCL antibody titres had stronger associations with thrombo-occlusive events, as well.

**Neurological manifestations: more than just stroke?**

Arterial thromboses commonly occur in the cerebral circulation of APS patients and lead to stroke or transient ischaemic attacks (TIA). Cerebral ischaemia most often presents due to middle cerebral artery occlusion but may affect any cerebral arterial territory (15). Cortical magnetic resonance imaging (MRI) findings are consistent with large vessel occlusion (Figure 2) (6,15). Stroke or TIA is the initial

| Table 1 Revised classification criteria (clinical) for the antiphospholipid syndrome |
|-----------------------------------------------------------------------------------|
| **Vascular thrombosis**<br>One or more episodes of arterial, venous or small vessel thrombosis in any tissue or organ<br>Thrombosis must be confirmed by appropriate imaging studies or histopathology<br>Thrombosis should be present without evidence of vessel wall inflammation on pathology |
| **Pregnancy morbidity**<br>One or more deaths of a normal fetus at or beyond the 10th gestational week. Normal morphology should be documented by ultrasound or direct exam, or<br>One or more premature births of normal neonates before the 34th gestational week<br>Eclampsia or severe pre-eclampsia<br>Placental insufficiency<br>Three or more unexplained consecutive spontaneous fetal losses before the 10th gestational week<br>Exclusion of other maternal hormonal and anatomic conditions and parental chromosomal causes |

Adapted from Miyakis et al. (3).

| Table 2 Revised classification criteria (laboratory) for the antiphospholipid syndrome |
|-------------------------------------------------------------------------------------|
| Lupus anticoagulant present in plasma on two or more occasions, at least 12 weeks apart detected according to international standards |
| Anticardiolipin (aCL) antibody (IgG or IgM isotype) in serum or plasma at medium-high titre (> 40 GPL or GML) measured by standardised ELISA assay on two or more occasions, at least 12 weeks apart |
| Anti-$\beta_2$-glycoprotein-I antibody (IgG or IgM isotype) in serum or plasma (> 99th percentile) measured by standardised ELISA on two or more occasions, at least 12 weeks apart |

Adapted from Miyakis et al. (3).
presentation in 20% of adults with APS. Case–control and prospective studies have shown robust associations between aPL antibodies and incident ischaemic strokes (16). These statistical relationships weaken in older populations and in recurrent ischaemic strokes. The Framingham heart study showed a hazard ratio (HR) of 2.6 for aCL antibodies in younger women (17). Thromboses were the leading cause of death in the latter 5 years of a prospective multi-national lupus cohort study. Strokes accounted for 11.8% of these events and were associated with aPL antibodies in a young predominantly female cohort (age 37 at study entry) (18). It is unclear whether similar risks exist for patients with isolated APS features. Conflicting data on associations between aPL antibodies and strokes may be due to study methodologies. Some studies included only baseline aPL testing, did not include lupus anticoagulant tests and enrolled patients who would not currently meet APS classification criteria.

The role of aPL in paediatric coagulopathies and strokes remains elusive. Most experts believe that isolated paediatric APS is a rare entity due to less prominent childhood prothrombotic risks. Yet, transient and often non-pathogenic aPL antibodies are also more prevalent in children and often seen after infections (7,19). Paediatric lupus patients appear to have higher rates of aPL antibodies compared with adults. Lupus anticoagulant positivity is associated with cerebrovascular disease in retrospective cohort studies. One small paediatric study detected increased aCl IgG antibodies in over 50% of patients with idiopathic cerebral ischaemia (20). A second study did not show an association between increased aCl IgG antibody titres and recurrent cerebral events (21). Few patients in this study had aCl IgG titres greater than 40 GPL units (per APS criteria). A European retrospective cohort of 28 paediatric APS patients revealed a high rate of progression to lupus in girls with APS (22). Recurrent thrombotic events were lessened in patients who received anticoagulant therapy in this cohort. The study also found a high rate of inherited thrombophilias (45% of patients) and proposed that aPL antibodies may serve as a ‘second vascular hit’ in children.

Coagulopathy and cerebral ischaemia may account for additional APS neurological features (Table 3). Chronic and recurrent small vessel ischaemic events predispose patients to early-onset multi-infarct dementia (15). Recurrent seizures are more prevalent in lupus patients with high titre aCL antibodies and may be associated with ischaemic changes. APS manifestations such as cognitive dysfunction and demyelination may have thrombotic and non-vascular mechanisms (12,15,23). Prospective studies associate persistent aPL 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 autoantibody titres (24,25). A small cross-sectional study revealed similar impairments in executive, memory and visuo-spatial domains in isolated APS patients with positive aCL antibodies (26). Antiphospholipid-mediated damage to white matter tracts and basal ganglia structures may account for multiple sclerosis-like features and movement disorders in APS patients (12,23).

**Treatment recommendations: assessing the evidence**

Venous thromboembolism, found in 32% of patients, is the most common initial manifestation of APS. Current available evidence favours warfarin administration with INR goals of 2–3 for patients with aPL antibodies and first venous thromboembolism (Table 4). Concerns about high thrombosis recurrence rates have led to a consensus that oral anticoagulation should be indefinite (27).

Retrospective studies with a predominance of lupus patients previously advocated high-intensity warfarin (INR > 3) therapy (28,29). Two recent randomised controlled trials (RCT) powered to
detect superiority of high-intensity warfarin challenged these conclusions. The studies had a predominance of young patients with isolated APS features (mean ages 41–42 years and less than 25% lupus patient enrolment). The majority of patients in these studies had venous thrombo-occlusive events (68–78%). The RCTs excluded patients with previous thromboses during anticoagulation and were plagued by low thrombosis rates during follow-up periods. Crowther et al. followed 114 patients for a mean of 2.7 years after randomisation to moderate or high-intensity warfarin (INR 2–3 vs. 3.1–4) (30). Only eight patients (7%) had recurrent thromboses in this study (six in the high-intensity group). The HR between high and moderate intensity groups did not reach statistical significance (HR 3.1, 95% CI 0.6–15). There were few recurrent arterial events during the follow-up period. Bleeding events were more frequent in the high-intensity group with an HR of 1.9 (95% CI 0.8–4.2). Finazzi et al. (WAPS study) randomised 109 patients to high-intensity warfarin (INR 3.5–4) or conventional anticoagulation (warfarin INR 2–3 or aspirin 100 mg) (31). There were only nine patients (8.2%) with recurrent thromboses in this study (six in the high-intensity group) during a mean follow-up of 3.6 years. The HR of 1.97 for the high-intensity group (95% CI 0.49–7.89) was not statistically significant. All bleeding complications were more frequent in the high-intensity group. An HR of 2.18 (95% CI 0.92–5.15) for bleeding in the high-intensity group approached statistical significance. Pooled data from both studies revealed a significant excess of minor bleeding events in high-intensity arms (Peto OR 2.3, 95% CI 1.16–4.58, p = 0.02).

Few studies have examined the efficacy of different therapies in the prevention of aPL antibody-associated strokes and arterial thromboses. General consensus favours treating patients with non-cerebral arterial thromboses with moderate-intensity warfarin (INR 2–3). Incident aPL-related cerebral arterial events are treated with either aspirin or moderate-intensity warfarin (INR 1.4–2.8) due to findings of

### Table 3

#### Neurological manifestations associated with antiphospholipid antibodies

| Stroke |
|--------|
| Transient ischaemic attack |
| Amaurosis fugax |
| Transient parasthesias |
| Cerebral venous sinus thrombosis |
| Ocular ischaemia |
| Acute ischaemic encephalopathy |
| Seizures |
| Cognitive impairment |
| Dementia |
| Optic atrophy |
| Transverse myelopathy |
| Multiple sclerosis-like disease |
| Guillian-Barré syndrome |
| Chorea |
| Migraine |
| Psychiatric disturbances |

#### Table 4

#### APS treatment recommendations

| Venous and non-cerebral arterial thrombosis |
|------------------------------------------|
| **Warfarin (INR 2-3)** |
| Indefinite treatment course |
| Cerebral arterial thrombosis |
| **Warfarin (INR 1.4-2.8) or aspirin** |
| Indefinite treatment course |

**Recurrent episode on therapy**

- Heparin (LMW or unfractionated)
- Warfarin with higher INR
- Warfarin plus antiplatelet therapy

### Table 3 Manifestations and potential pathogenic mechanisms of aPL in the nervous system

- **Thrombotic and ischaemic effects**
- **Thrombotic, immune, neurotransmitter effects**
the Antiphospholipid Antibodies and Stroke Study (APASS). An important caveat is that only 14% of study patients had moderate to highly positive aCL IgG or IgM titres and 20% had positive lupus anticoagulant tests. The published APASS analysis was only based on a single positive aPL determination. In APASS, a nested cohort study within the Warfarin vs. Aspirin Recurrent Stroke study (WARSS), death and incidence of thrombo-occlusive events were analysed by baseline antiphospholipid status and treatment group (32). 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. There were no observed increases in death or thrombotic events associated with aPL positivity in either treatment group. The respective relative risks (RR) for warfarin and aspirin were 0.99 (95% CI 0.75–1.31) and 0.94 (95% CI 0.7–1.28). An increased RR of 1.41 (95% CI .91, 2.36, p = 0.06) was found in patients with multiple positive antibody tests (lupus anticoagulant and aCL). Subgroup analyses for patients younger than 55 and those with cryogenic strokes revealed similar results. There were no differences in bleeding complications between aspirin and warfarin groups. The APASS study has raised questions about the utility of aPL antibody testing in older individuals with incident ischaemic strokes, as the majority of the patients with positive tests were of low titre and not predictive of recurrent events.

**APS stroke management: controversies**

Antiphospholipid syndrome experts debate the implications of recent prospective and randomised trials on cerebral thrombosis treatment. APASS conclusions based on single antibody measurement may not generalise to APS patients with persistent and severe disease processes. Some experts believe that the recent RCT studies did not adequately investigate therapies in aPL-associated arterial thromboses. Arterial disease reflects potent antibody effects and often leads to increased morbidity and mortality (33,34). Some researchers and clinicians still use high-intensity warfarin (INR 3–4) in patients with history of lupus, recurrent thromboses or initial arterial event. Prospective studies of warfarin and aspirin in aPL-related arterial diseases are needed to settle these debates.

There are no compelling data regarding treatments in the primary prevention of aPL-associated strokes in patients without previous thrombosis. A consensus panel concluded that aspirin therapy was a reasonable option in asymptomatic patients (35). Aspirin therapy is strongly recommended in patients with additional stroke risk factors such as lupus, hypertension, diabetes and hyperlipidaemia (16).

There is no evidence regarding optimal treatment of patients with recurrent thromboses while anticoagulated. A sub-therapeutic INR at time of thrombosis represents inadequate anticoagulation and not treatment failure (6). 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 lupus flare or those with diffuse microangiopathy (CAPS) may require intravenous immunoglobulin, plasma exchange and/or corticosteroid therapy (6). Anticoagulant regimens in paediatric APS are extrapolated from adult experiences. There are no expert opinions or trials that have examined warfarin, aspirin or heparin performance in childhood APS.

**Modifiable thrombotic risk factors and valvular heart disease**

The importance of modifiable vascular risk factors in the prevention of aPL-associated thromboses has been shown in 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 (36). Vascular events were independently predicted by aPL antibody, smoking, C-reactive protein and older age. A Japanese SLE cohort showed that hypertension and diabetes were independent risk factors of recurrent thromboses in addition to lupus anticoagulant status (37). The presence of additional prothrombotic risk factors may enhance the significance of aPL antibody in individual patients. Evaluations for prevalent adult thrombophilias such as factor V Leiden and methylenetetrahydrofolate reductase mutations may be warranted in some aPL-positive patients (4). Asymptomatic aPL-positive patients should be counselled about traditional cardiovascular risk factors and join smoking cessation programmes. Asymptomatic women with aPL positivity should be counselled about the additional hypercoaguable risks of oral contraception and pregnancy.

Recent studies in patients with lupus and isolated APS show associations between valvular heart disease and CNS manifestations. Lupus anticoagulant positivity and valvular anomalies (vegetation, thickening and regurgitation) were independent predictors of MRI-proven cerebrovascular disease in lupus patients (OR 5.3–10.6, p < 0.03) (38). Chronic coagulopathy and immune complex deposition may cause valvular
changes and embolisation to cerebral vessels. A retrospective European study showed an excess of valvular lesions in APS patients (isolated APS and lupus) with cerebrovascular disease (32% vs. 15%, \( p < 0.001 \)) (39). These studies suggest that echocardiography (preferably trans-oesophageal) be performed in patients with stroke and APS. Patients with valvular lesions may require oral anticoagulation to reduce recurrence of cerebral thrombo-embolic events.

### Additional treatment modalities

The complexities of caring for patients with APS include conflicting research findings, multifactorial pathogenic mechanisms, insensitivity of coagulopathy biomarkers and bleeding complications of oral anticoagulants. Concerns about warfarin safety drive research studies of targeted alternative therapies (Table 5). Statins are attractive agents in the treatment of APS patients. The agents block aPL-induced endothelial and platelet effects of binding protein-mediated intracellular signalling (40). Downstream endothelial and platelet effects of this inhibition include increased nitric oxide synthase (40). Statin therapy improves this inhibition include increased nitric oxide synthase (40). Downstream endothelial and platelet effects of binding protein-mediated intracellular signalling (40). These studies suggest that echocardiography (preferably trans-oesophageal) be performed in patients with stroke and APS. Patients with valvular lesions may require oral anticoagulation to reduce recurrence of cerebral thrombo-embolic events.

### Table 5 Future primary and secondary thrombosis treatments

| Biological targets in APS | Drug class |
|---------------------------|------------|
| Tissue factor expression  | ACE inhibitors |
| Endothelial cell effects  | Statins    |
| Platelet effects          | Adenosine uptake inhibitors |
| Immunosuppression          | Hydroxychloroquine |
| Anticoagulation            | Thrombin inhibitors |

Adapted from Crowther et al. (30) and Roubey (40). APS, antiphospholipid syndrome; ACE, angiotensin-converting enzyme.

### Conclusion and future research

Caring for APS patients remains a complex endeavour that requires individualised patient risk assessment. Clinicians must recognise the limits of available evidence-based guidelines. Traditional and evolving prothrombotic risks must be carefully interrogated in all APS patients. Subgroups of patients may require aggressive therapies and dosing regimens that may deviate from proposed consensus statements. Patients with lupus, previous strokes and multiple hypercoaguable risk factors require close clinical vigilance.

Antiphospholipid syndrome researchers should guide clinical efforts by designing studies that effectively measure treatment effects of new agents or dosing regimens. Novel endothelial biomarkers and functional coagulation assays may serve as integral research tools. Paediatric clinicians and research alliances will need to surmount similar challenges in even smaller groups of patients. Understanding the associations between aPL and non-stroke-related neurological disabilities warrants further research and funding.

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