Unusual manifestations of the antiphospholipid syndrome

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses (often multiple), recurrent fetal losses and is frequently accompanied by a moderate thrombocytopenia in the presence of antiphospholipid antibodies, namely lupus anticoagulant, anticardiolipin antibodies or anti-β2 glycoprotein-I antibodies. The APS can be found in patients with no clinical or laboratory evidence of another definable condition (primary APS) or it may be associated with other diseases, mainly systemic lupus erythematosus. Rapid chronological occlusive events, occurring over days to weeks, have been termed the catastrophic APS. Deep vein thrombosis, sometimes accompanied by pulmonary embolism, is the most frequently reported manifestation in this syndrome. Conversely, cerebrovascular accidents – either stroke or transient ischemic attacks – are the most common arterial thrombotic manifestations. Early and late fetal losses, premature births and preeclampsia are the most frequent fetal and obstetric manifestations. In addition, several other clinical features are relatively common in these patients, including thrombocytopenia, livedo reticularis, heart valve lesions, hemolytic anemia, epilepsy, myocardial infarction, leg ulcers and amaurosis fugax. However, a large variety of other clinical manifestations have been less frequently described in patients with the APS, with prevalences lower than 5%. In this article we will review some of these ‘unusual’ manifestations.

KEYWORDS: anticardiolipin antibodies | antiphospholipid antibodies | antiphospholipid syndrome | lupus anticoagulant

Large-vessel manifestations

Large peripheral arterial occlusions

The first paper to describe large peripheral arterial occlusions in detail in SLE patients was published in 1965 [3]. Several other reports of...
Table 1. Cumulative clinical features during the evolution of the disease in 1000 patients with antiphospholipid syndrome.

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral thrombosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>389</td>
<td>38.9</td>
</tr>
<tr>
<td>Superficial thrombophlebitis in legs</td>
<td>117</td>
<td>11.7</td>
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<tr>
<td>Arterial thrombosis in legs</td>
<td>43</td>
<td>4.3</td>
</tr>
<tr>
<td>Venous thrombosis in arms</td>
<td>34</td>
<td>3.4</td>
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<tr>
<td>Arterial thrombosis in arms</td>
<td>27</td>
<td>2.7</td>
</tr>
<tr>
<td>Subclavian vein thrombosis</td>
<td>18</td>
<td>1.8</td>
</tr>
<tr>
<td>Jugular vein thrombosis</td>
<td>9</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Neurologic manifestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>202</td>
<td>20.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>198</td>
<td>19.8</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>111</td>
<td>11.1</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>70</td>
<td>7.0</td>
</tr>
<tr>
<td>Multi-infarct dementia</td>
<td>25</td>
<td>2.5</td>
</tr>
<tr>
<td>Chorea</td>
<td>13</td>
<td>1.3</td>
</tr>
<tr>
<td>Acute encephalopathy</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>Transient amnesia</td>
<td>7</td>
<td>0.7</td>
</tr>
<tr>
<td>Cerebral venous thrombosis</td>
<td>7</td>
<td>0.7</td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>7</td>
<td>0.7</td>
</tr>
<tr>
<td>Transverse myelopathy</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Hemiballismus</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Pulmonary manifestations</strong></td>
<td></td>
<td></td>
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<tr>
<td>Pulmonary embolism</td>
<td>141</td>
<td>14.1</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>22</td>
<td>2.2</td>
</tr>
<tr>
<td>Pulmonary microthrombosis</td>
<td>15</td>
<td>1.5</td>
</tr>
<tr>
<td>Fibrosant alveolitis</td>
<td>12</td>
<td>1.2</td>
</tr>
<tr>
<td>Other (adult respiratory distress syndrome, pulmonary hemorrhage, pulmonary artery thrombosis)</td>
<td>7</td>
<td>0.7</td>
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<tr>
<td><strong>Cardiac manifestations</strong></td>
<td></td>
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<tr>
<td>Valve thickening/dysfunction</td>
<td>116</td>
<td>11.6</td>
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<tr>
<td>Myocardial infarction</td>
<td>55</td>
<td>5.5</td>
</tr>
<tr>
<td>Angina</td>
<td>27</td>
<td>2.7</td>
</tr>
<tr>
<td>Myocardiopathy</td>
<td>29</td>
<td>2.9</td>
</tr>
<tr>
<td>Vegetations</td>
<td>27</td>
<td>2.7</td>
</tr>
<tr>
<td>Coronary bypass rethrombosis</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>Intracardiac thrombus</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Intra-abdominal manifestations</strong></td>
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<tr>
<td>Renal manifestations (glomerular thrombosis, renal infarction, renal artery thrombosis, renal vein thrombosis)</td>
<td>27</td>
<td>2.7</td>
</tr>
<tr>
<td>Gastrointestinal manifestations (esophageal or mesenteric ischemia)</td>
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<td>1.5</td>
</tr>
<tr>
<td>Splenic infarction</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>Pancreatic infarction</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>Addison’s syndrome</td>
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<td>0.4</td>
</tr>
<tr>
<td>Hepatic manifestations (Budd–Chiari syndrome, small hepatic vein thrombosis)</td>
<td>7</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Cutaneous manifestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>241</td>
<td>24.1</td>
</tr>
<tr>
<td>Ulcers</td>
<td>55</td>
<td>5.5</td>
</tr>
<tr>
<td>Pseudovasculitic lesions</td>
<td>39</td>
<td>3.9</td>
</tr>
<tr>
<td>Digital gangrene</td>
<td>33</td>
<td>3.3</td>
</tr>
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</table>

*Data taken from [2]*.
large arterial occlusions and gangrene in SLE and ‘lupus-like’ patients who demonstrated aPL at some point during the course of their illness have subsequently been published [4–7].

Aortic occlusions
Several patients with an aortic arch syndrome and SLE have been reported [8–11], most of whom demonstrated aPL [9,10]. Occlusions of the abdominal aorta have also been documented [12,13].

Neurologic manifestations

Sneddon’s syndrome
The association of livedo reticularis with ischemic stroke and, on occasion, accompanied by hypertension, has been known as Sneddon’s syndrome since 1965 [14]. This may clearly be a manifestation of the primary APS [15,16]. However, the majority of these patients test ‘negative’ for aPL and Sneddon’s syndrome may well be a condition with an alternative pathogenesis, perhaps related to endothelial cell perturbation and dysfunction, leading to thrombotic lesions affecting vessels of the dermis and cerebral vasculature [17–19].

Acute ischemic encephalopathy
Acute ischemic encephalopathy has been observed in several patients with aPL [20,21]. Patients are acutely ill, confused and obtunded with an asymmetrical quadriplegia, hyperreflexia and bilateral extensor plantar responses. Seizures may also occur. Small cortical hypodensities are discernible on MRI scanning.

Cerebral venous & dural sinus thrombosis
Cerebral venous and dural sinus thrombosis have a diverse spectrum of clinical manifestations, the most common being headaches accompanied by
Papilledema, nausea, vomiting and visual field loss. Several such cases have been reported with aPL [21–26].

**Psychosis**
Several cases have been recorded where the APS is preceded by psychosis many years prior to the occurrence of thrombotic symptoms [27]. Increased aPL have indeed been documented in schizophrenic patients [28], as well as in patients suffering from major depressive illness [29–31].

**Cognitive defects**
Experimental work has found that neurologic and behavioural deficits in animal models are effects of the aPL. On immunofluorescence staining, immunoglobulin deposits have been observed in vessel walls of brain derived from these animals [32]. Four patients with APS who presented with rapidly progressive change in mental status, confusion, memory disturbance and emotional lability have also been reported [33].

**Transient global amnesia**
Transient global amnesia has been linked to aPL in one patient [34], and the authors suggested that aPL-linked ischemia may underlie the process.

**‘Pseudo-multiple sclerosis’**
Reports of several aPL-positive patients who were young and had fluctuating and recurrent neurologic events with focal and visual neurologic symptoms have been published. High signal lesions in the periventricular white matter on T2-weighted images resembled multiple sclerosis [35,36].

**Movement disorders**

**Chorea**
In a review of 50 cases of chorea in the APS [37], we found that 96% were female and that the mean age was 23 years. One episode of chorea was seen in 66% of the patients, while in 34% it was recurrent. Oral contraceptive-induced chorea, chorea gravidarium and post partum chorea occurred in 2–6% of patients. It was seen bilaterally or unilaterally, and occasionally commenced on one side, to reappear on the other side within weeks or months. Computed tomography scanning is usually normal, but infarcts outside the basal ganglia themselves might be seen. MRI findings were only reported in 13 of the 50 cases and infarcts in the caudate nuclei were only seen in three individuals. Steroids, haloperidol, aspirin and anticoagulation were used in several patients and all patients recovered, but the time taken for recovery varied from days to as long as a few months. Some authors have suggested that reversible immune-mediated responses, hormonally influenced in some, are the most likely pathogenesis of chorea, rather than a vascular hypothesis with thrombosis and infarction occurring [38–45]. Binding of autoantibodies to striatal interneurons may cause hypermetabolic dysfunction of these cells.

**Hemiballismus**
Hemiballismus is a rare movement disorder and has been recorded in one aCL-positive patient [46].

**Cerebellar ataxia**
Cerebellar ataxia may also rarely be related to the presence of aPL [47].

**Spinal syndromes**

**Transverse myelopathy**
Several papers have stressed the occurrence of transverse myelitis with the presence of the aPL [47–53]. Optic neuritis may occur simultaneously, presenting with rapid visual loss accompanied by orbital pain [54].

**Guillain–Barré syndrome**
A few patients with Guillain–Barré syndrome have been documented [55,56]. It has been suggested that aCL of the IgA isotype are associated with peak disease activity [57].

**Anterior spinal artery syndrome**
Sparing of the posterior columns occurs in anterior spinal artery syndrome, with the patient presenting with a flaccid paraplegia, sphincter disturbances and dissociated sensory impairment. Several cases with positive aCL have been documented [58–60].

**Ophthalmic complications**

**Cardiac manifestations**

**Coronary bypass graft & angioplasty occlusions**
Elevated aCL levels in patients who developed late bypass vein graft occlusions have been detected [68]. Another study reported increased IgA aCL levels in men with coronary artery disease who were treated with percutaneous trans-luminal coronary angioplasty and restenosed [69].
Cardiomyopathy

Multiple small vascular occlusions (‘thrombotic microvasculopathy’) are responsible for both acute and chronic cardiomyopathy seen in patients with aPL. Acute cardiac collapse (often together with respiratory decompensation) is frequent in patients with the catastrophic APS, and is one of the most common causes of death in this group of patients. Circulatory failure, as an isolated event, has also been reported [70,71], analogous to that seen with renal thrombotic microangiopathy. Chronic cardiomyopathy may be global or localised. Segmental ventricular dysfunction can supervene [72–74].

Intracardiac thrombus

Several patients with aPL have been reported who developed thrombi in the ventricular cavities [75–79]. Atrial thrombus might mimic atrial myxoma [80]. Occasionally, a clot may form on a normal mitral valve [81].

Complications of cardiovascular surgery

A 10% prevalence of a hypercoagulable condition has been detected on screening 158 patients with cardiovascular surgical procedures and these patients had a significantly higher incidence of early graft thrombosis [82]. Other authors identified 19 patients with aPL among 1078 treated for vascular surgical problems, while in a survey over a 2-year period [83], another group found that 26% of their patients were aPL positive and that they were 1.8 times more likely to have undergone previous lower-extremity vascular surgical procedures and 5.6 times more likely to have suffered occlusion of previous reconstructions [84]. In 1995, in a 5-year study, the authors identified 71 aPL-positive patients, of whom 19 had cardiovascular surgical procedures [85].

Pulmonary manifestations

Pulmonary arterial occlusions

Major pulmonary arterial thrombosis

Major pulmonary arterial thrombosis is distinctly rare and few such cases have been reported [86].

Pulmonary microthromboses

Unexpectedly, pulmonary microthromboses are also very uncommon in the APS, although originally suspected as being etiologically important in the pathogenesis of pulmonary hypertension in the presence of the aPL [87–89].

Acute respiratory distress syndrome

Several patients with the APS and acute respiratory distress syndrome (ARDS) have been reported [90,91]. A high frequency of ARDS in patients with catastrophic APS has also been described. It may be as a result of excessive cytokine production due to tissue damage seen in the catastrophic APS and is also part of the systemic inflammatory response syndrome, both in the context of infection and unrelated to precipitating factors. It has been described in patients with SLE-related APS and in primary APS.

Intra-alveolar pulmonary hemorrhage

Intra-alveolar pulmonary hemorrhage has been documented by several authors [88,92–96]. Coexisting pulmonary pathology such as pulmonary capillaritis, ARDS, microvascular thrombosis and bronchiolitis obliterans was present in several patients simultaneously.

Post-partum syndrome

A post-partum syndrome comprising spiking fevers and pleuritic chest pain associated with pleural effusion and patchy infiltration of the lungs on chest x-ray has been described [97,98].

Renal manifestations

Intrarenal vascular lesions (‘thrombotic microangiopathy’)

Termed ‘noninflammatory renal microangiopathy’ by some authors [99], intrarenal vascular lesions closely resemble those seen in malignant hypertension and other thrombotic microangiopathies such as those found in patients with systemic sclerosis, eclampsia, the thrombotic thrombocytopenic purpura–hemolytic uremic syndrome group of conditions and in patients with transplant rejection [100–103] (Figure 1).

Renal artery occlusions

Renal artery trunk lesions have been documented in several patients with APS. Severe hypertension is common and renal failure may result. Unilateral or bilateral renal artery occlusions have been documented. Renal infarction may develop [104–106].

Renal vein thrombosis

A relationship between thrombosis of the renal veins and the aPL has been suggested despite the fact that renal vein thrombosis is not uncommon in patients with a nephrotic syndrome, regardless of etiology [107–110].
"End-stage renal failure & hemodialysis
A total of 146 patients receiving dialysis for end-stage renal failure have been analyzed and it was found that having positive aCL predisposes to thrombotic events [111], in contrast to the bleeding tendency of end-stage renal patients. The association with repeated clotting of arteriovenous grafts has also been stressed by several authors [112–114].

Renal transplantation
Post-renal transplant thrombotic complications, including thrombotic microangiopathy, have been reported in some patients with aPL [115,116].

Pregnancy & post-partum syndromes
Renal failure occurring during pregnancy and, in particular, the post-partum period, may also be due to thrombotic microangiopathy. Several cases associated with aPL have now appeared in the literature [117–119].

Adrenal manifestations
Adrenal insufficiency is being increasingly recognized within the APS [120–132] and, although mainly reported in the adult literature [120–122], has also been documented in children and teenagers, the youngest being 10 years of age [123]. The mechanism for development of adrenal insufficiency seems to be a combination of adrenal vein thrombosis and/or hemorrhagic infarction and is usually bilateral. It has been proposed that any rise in adrenal venous pressure (e.g., such as occurs with venous thrombosis) would result in hemorrhage into the gland [127].

Hepatic manifestations
Budd–Chiari syndrome
Budd–Chiari syndrome is characterized by obstruction of large hepatic veins. Hepatic congestion and liver cell necrosis results [133–134]. Several case reports in patients with aPL have appeared [135–138].

Portal hypertension
The existence of portal hypertension in association with the aPL has been documented [139–143]. Several patients reported had a combination of both portal and pulmonary hypertension [139,144].

Obstruction of small hepatic veins (hepatic veno-occlusive disease)
Hepatic veno-occlusive disease is a condition characterized by nonthrombotic concentric narrowing of the lumen of small centrilobular veins by loose connective tissue and results in congestion and liver cell necrosis in the centrilobular areas [133]. Several patients with hepatic veno-occlusive disease and aPL have been reported. The condition is often associated with nodular hyperplasia of the liver and has also been reported in patients following bone marrow transplantation [144–146].

Nodular regenerative hyperplasia
A role for the aPL in the pathogenesis of nodular regenerative hyperplasia of the liver has been suggested [147,148] (Figure 2).

Hepatic infarction
Overt clinical hepatic infarction is rare but has occasionally been reported in the APS [148]. It seems to be not uncommon during pregnancy [149–151].

Digestive manifestations
Esophageal necrosis
A patient with a primary APS who thrombosed vessels at the lower end of the esophagus, resulting in necrosis, septic mediastinitis and death, has been documented [152].

Gastric ulceration
Progressive gastric ulceration with necrosis in a patient presenting with severe abdominal pain was found to be due to widespread occlusive vascular disease involving veins, small arteries and arterioles in one patient [153].
Small and large bowel vascular occlusions
Several cases of large bowel and intestinal infarctions in patients with aPL have been reported [154–161].

Mesenteric inflammatory vaso-occlusive disease
One patient with an unusual form of vasculitis involving the mesenteric vessels – mesenteric inflammatory vaso-occlusive disease – has been reported, who also developed an APS with deep vein thrombosis, thrombocytopenia and high titres of aCL [162]. The association of idiopathic mesenteric thrombosis and peripheral thrombosis has, in fact, been known for a long time [163].

Inflammatory bowel disease
Thromboembolic disease is a well recognized, although uncommon, complication of inflammatory bowel disease [164,165]. It has recently been reported that the presence of aPL may be associated with thrombosis in patients with ulcerative colitis and Crohn’s disease [166–170].

Occlusion of splenic vessels
Oclusion of splenic vessels has been reported in combination with other vascular occlusions and splenic infarction may supervene [154,171,172].

Obstetric manifestations
Maternal complications
Several reports have suggested that women with aPL are more likely to develop a post-partum cardio–pulmonary syndrome [173,174], chorea gravis-darum [37], post-partum cerebral infarct following aspirin withdrawal [173] and maternal death [174].

HELLP syndrome
A group of preclamptic patients have been defined with hemolysis, elevated liver enzymes and a low platelet count (HELLP) syndrome. Reports of an association between this syndrome and the aPL appeared in 1994 with a documentation of two cases [175], which both demonstrated aCL and appeared to be refractory despite delivery, corticosteroids and anticoagulation. Placental pathology and skin biopsy revealed diffuse deposition of fibrin with small-vessel thrombi. Plasma exchange resulted in resolution of the syndrome in these patients.

Obstearticular manifestations
Avascular necrosis of bone
A possible link between avascular necrosis of bone and aPL has been postulated [176], and this has been strengthened by reports of avascular necrosis of bone in patients with the primary APS who had not been exposed to glucocorticoid therapy at all [177–191].

Dermatologic manifestations
Cutaneous necrosis
Superficial skin necrosis has been reported by several investigators [192–195]. Necrosing livedo reticularis of the legs has been described in a patient with pulmonary hemorrhage [196] and widespread skin necrosis in a patient with AIDS and aPL has been documented [197]. Widespread cutaneous necrosis is associated with massive thrombosis of small and medium-sized dermal vessels and has also been reported with the primary APS [198], with SLE [193,199], with rheumatoid arthritis [200] and in mycosis fungoides [201]. Painful cutaneous necrosis has been described on the cheeks and earlobes of a patient with lupus anticoagulant [202]. A patient with skin necrosis occurring during coumadin therapy who additionally had an acquired protein S deficiency and primary APS has also been documented [203].

Macules & nodules
Erythematous macules and painful skin nodules occurring in aPL-positive patients have been reported. These lesions are due to thrombotic skin disease, are located on the palms, soles and fingers and do not disappear on pressure [202,204]. These painful lesions have been reported as improving with salicylate therapy [205]. One patient with lymphocyte vasculitis, thrombosis and aCL was also documented [206].

Figure 2. Hepatic nodular regenerative hyperplasia.
Multiple subungual hemorrhages
Multiple subungual hemorrhages have been reported in the APS [207], in the absence of infective bacterial endocarditis (pseudo-infective endocarditis) [208], dependent on warfarin withdrawal and the appearance of catastrophic APS [209], with the administration of oral contraceptives and during pregnancy [207], and with amaurosis fugax [210,211].

Gangrene & digital necrosis
Cutaneous ischemic symptoms may culminate in digital gangrene and aPL-associated gangrene [7].

Conclusion
The many manifestations summarized in this article may not be statistically significantly related to the presence of the aPL or indeed be considered as ‘definite’ manifestations of the APS according to the classification criteria. However, as more cases are reported, the statistical evidence for these associations may become more definite. Many of these conditions are themselves uncommon and the demonstration of aPL has enabled us to more easily understand their pathogenesis, until now unexplained and complex.

The expanding spectrum of the association of a large variety of clinical events with the presence of the aPL, not all of which are associated with the presence of underlying thrombotic lesions (e.g., chorea), is evidence of the multifactorial actions of this group of antibodies and doubtless, as more cases are reported and published in the future, the unravelling of this unique group of disorders will take place.

Therapy, with the introduction of novel compounds affecting different phases of the coagulation cascade, will also be refined and hopefully the need for long-term anticoagulation therapy with all its difficulties and attendant complications will fall away.

Future perspective
The etiology of APS has been studied extensively. However, a key question remains unsolved: is the etiology single or multiple? A ‘two-hit hypothesis’ has been suggested to explain the clinical observation that thrombotic events occur only occasionally in spite of the persistent presence of aPL. The aPL (first hit) increases the thrombophilic risk and the clotting takes place in the presence of another thrombophilic condition (second hit). It has been suggested that infectious processes may be the second hit since they frequently precede the full-blown picture of the syndrome and may be the initiator of the catastrophic subtype. Innate immunity receptors (i.e., toll like receptors) and mediators (complement) involved in sensing microbial agents might synergize and contribute in triggering the clotting event. However, the infectious etiology of APS is not limited to the triggering effect of infectious processes. In fact, it has been shown that antibodies against the main aPL antigenic targets, such as β2 glycoprotein-I, may be synthesized by B cell clones cross-reacting with epitopes expressed on infectious agents as the result of a molecular mimicry between exogenous molecules and β2 glycoprotein-I. Whether an individual will develop APS will depend mainly on his/her genetic predisposition, which might or might not favor the production of the cross-reacting autoantibodies.

Therefore, the questions remains if there are additional etiological factors for APS. Are there other environmental factors that are responsible for inducing APS, such as drugs or tumors? Are there other stimulants of the innate immune system driving it toward an overt APS, such as redox effect? If persistent positivity for aPL represents a condition necessary but not sufficient by itself to induce the clinical manifestations of the syndrome, is there a genetic background for explaining why a positive aPL carrier develops thrombotic events or remains asymptomatic? May the same genetic background explain why the catastrophic variant occurs in some cases only? The presence of aPL, but not the clinical manifestations of the disease, has been associated with MHC genes, while concomitant genetic thrombophilic conditions were reported to increase the ultimate risk of thrombotic events.

Financial & competing interests disclosure
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Executive summary

- The classical clinical picture of the antiphospholipid syndrome (APS) is characterized by venous and arterial thromboses, fetal losses and thrombocytopenia, in the presence of antiphospholipid antibodies (aPL). Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations.

- Deep vein thrombosis, sometimes accompanied by pulmonary embolism, is the most frequently reported manifestation in this syndrome (38.9%). Cerebrovascular accidents – either stroke (19.8%) or transient ischemic attacks (11.1%) – are the most common arterial thrombotic manifestations. Early fetal loss (35.4%), late fetal loss (16.9%), premature birth (10.6%), and preeclampsia (9.5%) are the most frequent fetal and obstetric manifestations.

- Several other clinical features are relatively common in these patients, including thrombocytopenia (29.6%), livedo reticularis (24.1%), heart valve lesions (11.6%), hemolytic anemia (9.7%), epilepsy (7%), myocardial infarction (5.5%), leg ulcers (5.5%) and amaurosis fugax (5.4%).

- However, a large variety of clinical manifestations have been occasionally described in patients with the APS, with prevalences lower than 5%. Virtually any organ, system or tissue of the body can be affected and the APS be manifested in such diverse conditions as chorea, intracardiac thrombus, acute respiratory distress syndrome, Addison’s disease, Budd–Chiari syndrome, avascular necrosis of bone or preeclamptic patients with hemolysis, elevated liver enzymes and a low platelet count (HELLP syndrome), to name just a few.

Bibliography

Papers of special note have been highlighted as:
* of interest
** of considerable interest


** Largest survey of antiphospholipid syndrome (APS) patients describing the prevalence of the main clinical manifestations of this syndrome.


* Largest series of APS patients with gangrene and amputation of digits or limbs.


Cervera & Espinosa


* Largest series of APS patients with chorea.


Unusual manifestations of the antiphospholipid syndrome


** Original description of the catastrophic APS.


170 Asherson RA, Khamash MA, Ordí-Ros J et al.: The ‘primary’ antiphospholipid


