Thrombotic events most often occur in the venous system, particularly in the lower limb deep veins. Arterial thrombosis is less common but predominantly involves the cerebral vessels. Several neurologic syndromes have been described in patients with APS.

Cerebrovascular disease, mostly a consequence of the hypercoagulable state associated with APS, might be increased, in some patients, by the coexistence of other risk factors, such as hypertension, smoking and oral contraceptives.

The APS has been classified as secondary if it occurs in a patient with systemic lupus erythematosus (SLE) or another autoimmune disease, and primary (PAPS) in the absence of autoimmune disorders.

Clinically, primary and secondary APS are indistinguishable and the development of SLE in patients with primary APS of many years’ duration has been well described.

The aim of this overview is to review the clinical features of neurological manifestations associated with APS.

**Main Neurological Syndromes (Table I)**

**Cerebral ischemia**

Cerebral ischemia is the most common arterial thrombotic manifestation of APS. High titers of aCL have been associated with recurrent events in patients with primary APS and secondary antiphospholipid antibodies syndrome. Many authors have reported that aPL are associated with an increased risk for episodes of cerebral ischemia. Ischemic events can occur in any vascular cerebral territory. Angiography demonstrates intracranial branch or trunk occlusion or is normal in
about on-third of patients so investigated\(^{15}\).

Many cardiac valvular lesions have been associated with aPL: in a large consecutive autopsy series, a higher incidence of cardiac valvular abnormalities and thromboembolic lesions were found in patients with aPL\(^ {15,16}\). The greater risk for thrombosis in antiphospholipid syndrome is due to the following features: cardiolipin or \(\beta_2\)-GP1 immunoreactivity of the IgG2 isotype and phosphatidylserine immunoreactivity\(^{17}\). In addition Specker et al. have demonstrated that cerebral microemboli detected by transcranial doppler are found in patients with APS and that they correlate with a history of cerebral ischemia\(^ {18}\).

Cerebrovascular ischemia
Stroke
Transient ischemic attack
Cerebral venous sinus thrombosis

Dementia
Acute ischemic encephalopathy
(with or without Sneddon’s syndrome)

Seizures
Transverse myelitis
Chorea

Other neurological syndromes
Transient global amnesia
Psychiatric disorders
Ocular ischemia
Guillan-Barré syndrome

Migraine
Although in SLE patients the prevalence of both migraine and aPL are increased over general population, the prevalence of aPL in subjects with migraine does not appear to be increased. The largest case-control study to date has failed to demonstrate an association of aCL immunoreactivity in patients under 60 years of age with either migraine with aura, migraine without aura, or transient focal neurological events compared to controls\(^ {22-23}\).

Seizures
In SLE patients seizures may be induced by aPL-associated cerebral infarction\(^ {25}\). There are some experimental data that support the primary involvement of immune system for seizures associated with aPL\(^ {26}\). Antiphospholipid antibodies have been demonstrated to bind directly to cat and murine brain and aPL have been shown to reduce a GABA receptor-mediated chloride current in snails neurons\(^ {25}\). This inhibitory effect suggests a direct and reversible mechanism through which aPL might lower seizure threshold.

Transverse myelopathy
LaValle et al. reported transverse myelitis in 12 SLE patients, all of them having aPL immunoreactivity\(^ {27}\). Six also had other APS clinical features such as thrombocytopenia, live-
do reticularis, thrombosis and leg ulcers. The pathophysiology of spinal cord damage in aPL associated myelopathy is uncertain: both ischemia and an antibody-mediated interaction have been suggested.

Chorea

Chorea can occur in both primary and secondary APS and is often the presenting clinical feature. Reversible chorea dysfunction can be related to striatal binding of aPL. This hypothesis suggested by Asherson et al. is supported by several recent case reports describing patients with aPL-associated chorea studied serially using PET.

Discussion

Originally recognized in patients with SLE, APS was later described in a number of cases who did not fulfill four American Rheumatism Association criteria for the classification of SLE and did not show any clinical or laboratory features of other disorders. These observations led to the definition of a “primary” antiphospholipid syndrome (PAPS). The differential diagnosis between SLE-related APS and PAPS may be problematic. To this regard, Piette et al. have formulated a number of exclusion criteria to distinguish these conditions. However, the relationship between SLE and PAPS is still unclear since, in some cases, PAy may antedate the development of a “lupus-like disease” or full-blown SLE.

The high frequency of neurologic complications in PAPS suggests a peculiar susceptibility of the central nervous system (CNS) to aPL. Neurologic dysfunctions may in part reflect the systemic hypercoagulable state associated with aPL. Ischemic arteriopathy in medium-size vessels has been described angiographically and thrombosis of small vessels without signs of vasculitis has been demonstrated histologically. It has also been suspected that aPL react with brain lipids, such as cephalin or sphingomyelin. Indeed, rare complications such as chorea are not consistent with vascular changes and neuronal function derangement has been postulated. Experimental studies have demonstrated that aPL purified from pooled serum samples of SLE patients have inhibitory effects on cultured normal rat brain astrocytes and bind brain tissue. It was therefore hypothesized that the anticardiolipin antibodies may impair the blood-brain barrier, thus allowing circulating autoantibodies to access and damage the brain tissue. However, in patients with PAPS and cerebral involvement, the frequency of serum antineuronal antibodies was not found to be significantly different from that of patients without CNS disease, whereas it was significantly lower than that found in SLE patients with CNS involvement.

One or more of these mechanisms could explain not only the well known clinical syndromes associated with aPL but also the evidence of cerebral atrophy. Recently, Chapman et al. demonstrated that purified IgG from APS patients permeabilize and depolarize brain synaptoneurosomes: these results may explain some of the non-thromboembolic central nervous system manifestations and lead to irreversible damage and neuronal loss.

With regard to the treatment of APS, oral anticoagulant therapy is an effective secondary prophylaxis, while steroids and immunosuppressive drugs have not provided long-term benefit.

In conclusion, in patients with neurologic dysfunctions, an immunological screening comprehensive of aPL determination should always be performed in order to reveal an APS with unusual presentation.

References


34) Harris En, Gharavi AE, Boey ML, Patel BM, Mackworth-Young GC, Loizou S. Anticardiolipin antibodies: detection by radioimmunoassay and...


