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Neurological involvement in antiphospholipid antibodies syndrome (APS)

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Abstract. – **Antiphospholipid antibodies (aPL) have been most strongly associated with a syndrome (APS) characterized by venous and/or arterial thrombosis, thrombocytopenia, recurrent fetal losses and a variety of non-thrombotic and thrombotic neurological disorders.**

Cerebral ischemia associated with aPL is the most common arterial thrombotic manifestation. Other neurological syndromes, such as cognitive dysfunction, dementia, psychosis, depression, seizures, chorea and transverse mielopathy, have all been associated with antiphospholipid antibodies.

Key Words:

Antiphospholipid antibodies, Thrombosis, Stroke, Migraine, Seizures, Chorea, Transverse myelitis.

Introduction

Antiphospholipid antibodies syndrome (APS) is characterized by venous and/or arterial thrombosis, thrombocytopenia, recurrent fetal losses and a variety of neurologic disorders. Antiphospholipid antibodies (aPL) are a family of autoantibodies detectable in assays measuring immunoreactivity to cardiolipin (aCL) and other negatively charged phospholipids alone or in the presence of β_2-glycoprotein1 (β_2-GP1) or other protein cofactors[1] or by their ability to prolonge phospholipid-dependent coagulation assays (lupus anticoagulants-LAC). Repeated positive anticardiolipin and/or LAC tests are generally accepted as confirmatory assays for APS[2,3].

The presence of all these clinical and laboratory findings is not needed to make diagnosis of APS[4]. However, when the presenting symptoms are neurologic abnormalities alone, appropriate diagnosis may be problematic.

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[5]. Several neurologic syndromes have been described in patients with APS[6,7]. 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[8].

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[9]. High titers of aCL have been associated with recurrent events in patients with primary[10] and secondary antiphospholipid antibodies syndrome[11]. Many authors have reported that aPL are associated with an increased risk for episodes of cerebral ischemia[12,13]. Ischemic events can occur in any vascular cerebral territory[14]. Angiography demonstrates intracranial branch or trunk occlusion or is normal in

Table I. Main neurological syndromes associated with aPL.

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

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 β_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].

Cerebral venous sinus thrombosis

Carhuapoma et al. have recently suggested that aPL may be an important factor contributing to cerebral venous sinus thrombosis (CVT) even in the presence of other potential risk factors for thrombosis, including the syndrome of activated protein C resistance due to factor V Leiden mutation[19].

Cognitive dysfunction, dementia, depression and psychosis

Recurrent stroke in patients with livedo reticularis (Sneddon's syndrome) has been associated with aPL[20]. This syndrome is also frequently accompanied by dementia on the basis of multiple infarctions.

Coull et al. described three stages of neurological involvement:

a) Prodromal symptoms such as hedeache preceding focal neurological manifestations by years;
b) Recurrent focal neurological deficits secondary to recurrent cerebral ischemia;
c) Progressive cognitive impairment leading to severe dementia[21].

Memory disturbance or disability to perform activities of daily living were found in 50% of patients: dementia was described in over half of patients with disability and correlates with increasing severity of brain magnetic resonance imaging lesions[21].

Depression and psychosis have been associated with aPL but is not clear whether this finding is simply related to the use of drugs-induced antiphospholipid antibodies such as chlorpromazine[22-23].

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[24].

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[26]. This inhibitory effect suggests a direct and reversible mechanism through wich aPL might lower seizure threshold.

Transverse myelopathy

Lavalle et al. reported tranverse 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 hypotesis suggested by Asherson et al.[28] is supported by several recent case reports describing patients with aPL-associated chorea studied serially using PET[29].

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 classificaton 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)[30]. 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[31]. However, the relationship between SLE and PAPS is still unclear since, in some cases, PAPS may antedate the development of a "lupus-like disease" or full-blown SLE[32].

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[6] and thrombosis of small vessels without signs of vasculitis has been demonstrated histologically[33]. It has also been suspected that aPL react with brain lipids, such as cephalin or sphingomyelin[34]. Indeed, rare complications such as chorea are not consistent with vascular changes and neuronal function derangement has been postulated[35]. 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[36]. 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[36]. 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[37].

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[38]. 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 manifefestations and lead to irreversible damage and neuronal loss[39].

With regard to the treatment of APS, oral anticoagulant therapy is an effective secondary prophylaxis[40], while steroids and immunosuppressive drugs have not provided long-term benefit[5].

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

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