7 Cerebral Disease Other than Stroke and Transient Ischemic Attack in Antiphospholipid Syndrome

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Central nervous system (CNS) involvement is one of the most prominent clinical manifestations of antiphospholipid (Hughes) syndrome (APS) and includes arterial and venous thrombotic events, psychiatric features, and a variety of other non-thrombotic neurological syndromes.

In 1983, Hughes, in his original description of the syndrome, highlighted the importance of cerebral disease in patients with APS [1]. In the early 1980s, his group reported the presence of antiphospholipid antibodies (aPL) in association with cerebrovascular accidents, intractable headache or migraine, epilepsy, chorea, idiopathic transverse myelitis, Guillain-Barré syndrome, and dementia [2–5].

The full impact of APS on neurology is now becoming increasingly recognized [6]. The range of neurological features of APS is comprehensive and includes focal symptoms attributable to lesions in a specific area of the brain as well as diffuse or global dysfunction [7–10]. Table 7.1 summarizes the wide spectrum of CNS manifestations that have been reported in association with aPL.

Although the mechanism of neurological involvement in APS is thought to be thrombotic in origin and cerebral ischemia is the most common manifestation [9], a number of other neuropsychiatric manifestations, including chronic headache, dementia, cognitive dysfunction, psychosis, depression, transverse myelitis, multiple sclerosis-like disease, chorea, and seizures have been associated with the presence of aPL [4, 6, 10–14]. Many of these manifestations cannot be explained solely by hypercoagulability and it is possible that some of them (e.g., cognitive dysfunction, seizures, chorea) may have more complex causes.

It is not completely understood why the CNS is particularly vulnerable in patients with APS.

There is an increasing body of evidence which supports the hypothesis that aPL may also have more direct effects on the brain [11]. It has been shown that aPL bind neurons, glial cells, and myelin and disrupt their function [15, 16]. aPL also interfere with endothelial cell function and promote the procoagulant activity of endothelial cells [17–20]. Lai and Lan [21] found high levels of IgG anticardiolipin antibodies (aCL) in cerebrospinal fluid of systemic lupus erythematosus (SLE) patients with CNS involvement, including headache, acute psychosis, and cognitive impairment, suggesting that aPL may also produce direct neurologic tissue damage

Table 7.1. Neuropsychiatric manifestations associated with the presence of antiphospholipid antibodies.

Cerebrovascular disease
Transient ischemic attacks
Ischemic stroke
Acute ischemic encephalopathy
Cerebral venous thrombosis
Seizures
Headache
Chorea
Multiple sclerosis–like syndrome
Transverse myelitis
Idiopathic intracranial hypertension
Other neurological syndromes
Sensorineural hearing loss
Guillain-Barré syndrome
Transient global amnesia
Ocular syndromes
Dystonia–Parkinsonism
Progressive supranuclear palsy
Cognitive dysfunction
Dementia
Other psychiatric disorders
Depression
Psychosis

through immune-mediated mechanisms. Animal models are providing important insights in some of the underlying mechanisms for CNS dysfunction in APS [22–24].

In this chapter we will attempt to highlight the broad spectrum of the neuropsychiatric manifestations that have been reported in association with aPL with a particular emphasis on those without a well-defined underlying thrombotic mechanism. Cerebrovascular disease will be described in another chapter of this book.

Seizures

A number of studies – mainly in SLE patients – have confirmed the original observation of Mackworth-Young and Hughes in 1985 [25] of the association between aPL and seizures [14, 26–32].

Herranz et al [27] found that moderate-to-high titers of IgG aCL were associated with seizures in SLE patients, suggesting an important role for these antibodies in the aetiopathogenesis of this manifestation. Liou et al [29] confirmed the association between epilepsy and aCL in 252 SLE patients recruited in a prospective study, where the odds ratio of developing seizure for those patients who had a high level of aCL was 3.7 when compared with those without a detectable level of aCL.

Our most recent experience confirmed a strong association between the presence of aPL and seizures in a series of 323 SLE patients [32]. We found that the prevalence of aCL was higher in patients with seizures than in those without. The association of seizures with aCL remained significant after excluding 47 patients with cerebrovascular accidents. We also showed that IgG and IgM aCL were both independently associated with cerebrovascular accidents and seizures by multivariate analysis.