6 Cerebral Ischemia in Antiphospholipid Syndrome

Debendra Pattanaik and Robin L. Brey

Introduction

Central nervous system (CNS) involvement is common in antiphospholipid antibody syndrome (APS). In fact neurological manifestations were only second to venous thrombosis in a recently published prospective cohort of 1000 patients with APS [1]. In addition, some of the most debilitating clinical aspects of APS are the neurological and neuropsychiatric manifestations. Clinical manifestations of APS associated with the CNS include thrombo-occlusive events, psychiatric manifestations, and a variety of other non-thrombotic neurological syndromes [2] (see Table 6.1). Nevertheless, the specific role of antiphospholipid antibodies (aPL) in the CNS remains one of the least understood aspects of this syndrome. The mechanism of neurological involvement in patients with APS is thought to be primarily thrombotic in origin. However, there are many neurological syndromes where no structural lesions are evident in imaging studies of brain, suggesting aPL-mediated mechanisms other than thrombosis may be playing a role. Several investigators have found an interaction between aPL and nervous system tissue [3, 4]. aPL may interfere with endothelial cell function and promote procoagulant activity of endothelial cells [5–8]. IgG fractions from patients with aPL also increase mononuclear cell adhesion to human umbilical vein endothelial cells [9]. The pathogenic role of aPL in the development of thrombosis is supported by animal studies [8,

Table 6.1. Neurologic syndromes associated with antiphospholipid antibodies.

Cerebrovascular ischemia Stroke Transient ischemic attack Cerebral venous sinus thrombosis	Chorea
Ocular ischemia	Transverse myelopathy
Dementia Acute ischemic encephalopathy With Sneddon's syndrome Without Sneddon's syndrome	Guillain–Barré syndrome
Atypical migrainous-like events	Diabetic peripheral neuropathy
Seizures	Sensorineural hearing loss Sudden onset Progressive
	Transient global amnesia
	Psychiatric disorders
	Orthostatic hypotension

10–14]. Blank and colleagues showed that bacterial peptides homologus with β_2-glycoprotein I (β_2-GPI) induce pathogenic anti–β_2-GPI along with APS manifestations in mice and proposed a mechanism of molecular mimicry in experimental APS [13]. These investigations in animal models are useful for a better understanding the pathogenic mechanisms and to test new therapies for APS.

Cerebral Ischemia

Cerebral ischemia associated with aPL is the most common arterial thrombotic manifestation [15–17]. Stroke and transient ischemic attacks (TIAs) are considered the second most common clinical manifestations of primary antiphospholipid syndrome (PAPS) after venous thrombosis [1]. The average age of onset of aPL-associated cerebral ischemia is several decades younger than the typical cerebral ischemia population [18]. Cerebral ischemic events can occur in any vascular territory (see Fig. 6.1) [19], but in general the territory of the middle cerebral artery is more affected. A link has been postulated between cervico-cranial artery dissection and APS [20]. Though infrequent, cardiac emboli may be another cause of cerebral ischemia in patients with aPL. Cerebral ischemic events are more frequent in patients with valvular heart disease. The prevalence of valvular abnormalities, particularly left sided valve lesions, is higher in systemic lupus erythematosus (SLE) patients with aPL than in those without aPL [21, 22]. A study by Khamastha and colleagues [22] showed that patients with SLE and aPL have an increased frequency of mitral valve vegetations and mitral regurgitation than aPL-negative patients (16% vs. 1.2% and 38% vs. 12%, respectively). These may represent a potential cardiac source of stroke [21–23]. In a large consecutive autopsy series, a higher incidence of

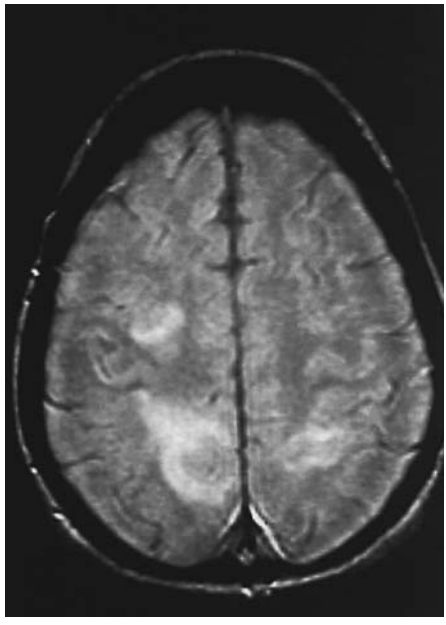

Figure 6.1. Brain magnetic resonance imaging (MRI) study showing multiple strokes in a young woman with antiphospholipid antibodies, strokes, and seizures.