Central nervous system (CNS) involvement is common in patients with antiphospholipid (Hughes) syndrome (APS). In 1983 Hughes, in his original description of the syndrome, stressed the importance of cerebral features in these patients [1]. He highlighted the frequency of intractable headache or migraine, epilepsy, chorea and cerebrovascular accidents (transient ischaemic attacks or visual field defects or progressive cerebral ischaemia) [2].

In the early 1980s the same group also reported the presence of antiphospholipid antibodies (aPL) in patients with idiopathic transverse myelopathy [3], Guillain–Barré syndrome [4] and dementia [5] suggesting that aPL-associated neuropsychiatric involvement can be comprehensive [6]. Although the mechanism of neurologic involvement in patients with APS is thought to be thrombotic in origin and cerebral ischaemia associated with aPL is the most common arterial thrombotic manifestation, a number of other neuropsychiatric manifestations, including optic atrophy, chronic headache, dementia, cognitive dysfunction, psychosis, depression, transverse myelopathy, multiple sclerosis-like disease, chorea and seizures have been associated with aPL [7]. Table 1 summarizes CNS manifestations reported to be associated with the presence of aPL.

Many of these manifestations cannot be explained solely by hypercoagulability and can have more complex causes. For instance, in many patients with chorea, focal lesions on CT scan have not been found [8, 9], throwing doubt on a purely thrombotic cause. aPL may have more direct effects; they may bind neurons or glial cells and disrupt their function. Sun et al. [10] found that anticardiolipin antibodies (aCL) bind to mouse brain tissue and may inhibit astrocyte proliferation in vitro. Khalili and Cooper found that patients with systemic lupus erythematosus (SLE) with elevated aCL have high binding to myelin [11]. There is evidence that aPL may interfere with endothelial cell function and promote the procoagulant activity of endothelial cells [12]. Simontov et al. [13] demonstrated that IgG fractions from patients with aPL increase mononuclear cell adhesion to human umbilical vein endothelial cells (HUVEC).

More recent studies showed that anti-β2GPI antibodies bind and activate endothelial cells through the adherent cofactor β2GPI, probably leading to a procoagulant state [14]. These studies indicate that aPL may prime the endothelium, making the vasculature prone to thrombosis and leucocyte adhesion. An important question that remains unanswered is why the brain and CNS seem to be particularly vulnerable in patients with APS.

The pathogenic role of aPL in the development of thrombosis is supported by data coming from animal models. APS has been induced after immunization of
normal mice with aCL or β2-GPI [15]. Furthermore, immunization of BALB/c mice with monoclonal aCL resulted in APS with neurological dysfunction and impaired motor co-ordination [16]. Recently the pathogenic potential of microbial pathogens carrying sequences with a specific hexapeptide has been investigated. Blank et al. [17] showed that bacterial peptides homologous with β2-GPI induce pathogenic anti-β2-GPI along with APS manifestations in mice and proposed a mechanism of molecular mimicry in experimental APS. These investigations in animal models are useful for a better understanding of the pathogenic mechanisms and to test new treatments for APS.

Cerebrovascular disease

aPL and cerebral ischaemia in patients with primary (PAPS) and SLE-associated APS

Strokes and transient ischaemic attacks (TIAs) are considered the second most common clinical manifestations of PAPS after venous thrombosis [18]. Cerebrovascular disease is the most frequent neurological manifestation in patients with aPL, who are younger if compared with the general population [19]. The association between cerebrovascular disease and aPL was described in the early studies [5, 20] and later confirmed by many other authors [21].

In 1984 Harris et al. [20] reported 15 patients, 13 with SLE and two with a ‘lupus-like’ illness who developed cerebral infarction. All 15 patients were shown to have elevated aCL levels using a newly devised solid-phase radioimmunoassay [22]. The lupus anticoagulant (LA) was detected in all 11 patients tested. The authors proposed that aCL and the LA represent a population of aPL capable of causing cerebral vascular injury and thrombosis resulting in cerebral infarction, proposing a pathogenic role of these antibodies in autoimmune disorders.

Episodes of cerebral ischaemia, mainly focal, can be transient or permanent. Recurrent disease often leads to multifocal deficits. Amaurosis fugax [21], transient paraesthesias, motor weakness, vertigo and transient global ischaemia [23] can all be expressions of TIAs. TIAs are often recurrent and may precede cerebral infarction by weeks or months. They can also occur in the absence of cerebral infarction.

An ischaemic stroke can be isolated or multiple and recurrent. The risk for recurrent stroke appears to be increased in APS patients and multiple events can occur after the first cerebral ischaemic episode [24]. Generally the territory of the middle cerebral artery is more affected [7], but ischaemic events can occur in any vascular territory [25].

A chronic multifocal disease can produce multi-infarct dementia [21]. This dementia, generally associated with a loss of cognitive functions and impairment of skills, concentration, memory dysfunction, language impairment and judgemental defects, does not present with peculiar characteristics. It can be difficult to differentiate from other kinds of dementia such as Alzheimer’s disease, senile dementia or metabolic/toxic conditions involving the brain.

Although probably infrequent, cardiac emboli may be another cause of cerebral ischaemia in patients with aPL. Devinsky et al. [26] reported 5/50 SLE patients who developed cerebral emboli from Libman–Sacks endocarditis. Another possible source can be the heart chambers themselves or the internal carotid artery. Cerebral ischaemic events are more frequent in patients with valvular heart disease. It has been shown that the prevalence of valvular abnormalities, particularly left-sided valve lesions, is higher in SLE patients with aPL than in those without aPL. Khamashita et al. [27] 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). In this study, 9/50 patients with mitral valve disease had had cerebrovascular occlusions during follow-up, showing that valvular lesions can be a source for emboli and a possible cause of ischaemic stroke in aPL patients, as reported by other authors [28, 29].

Brain MRI in aPL patients with ischaemic stroke shows cortical abnormalities consistent with large vessel occlusion. aPL patients often present small foci of high signal in brain white matter at MRI, which are often defined as consistent with the presence of small vessel disease. Not only are these lesions non-specific but their aetiology is unclear. Larger size and atypical topographic distribution of these lesions in aPL patients may be also consistent with demyelination and sometimes difficult to differentiate from MRI pictures in multiple sclerosis (MS) [30].

There have been several reports of the association of recurrent episodes of cerebral ischaemia in patients with livedo reticularis—known as Sneddon’s syndrome—with aPL, leading to the understanding that a ‘subset’ of patients diagnosed as having Sneddon’s syndrome can be also diagnosed as having APS [31]. Kalashnikova

### Table 1. Central nervous system manifestations associated with the presence of antiphospholipid antibodies

<table>
<thead>
<tr>
<th>CNS involvement in the antiphospholipid syndrome</th>
<th>201</th>
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<tbody>
<tr>
<td>Cerebrovascular disease</td>
<td>201</td>
</tr>
<tr>
<td>Transient ischaemic attacks</td>
<td></td>
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<tr>
<td>Ischaemic strokes</td>
<td></td>
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<tr>
<td>Acute ischaemic encephalopathy</td>
<td></td>
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<tr>
<td>Cerebral venous thrombosis</td>
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<tr>
<td>Epilepsy</td>
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<tr>
<td>Headache</td>
<td></td>
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<tr>
<td>Chorea</td>
<td></td>
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<tr>
<td>Multiple sclerosis</td>
<td></td>
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<tr>
<td>Transverse myelitis</td>
<td></td>
</tr>
<tr>
<td>Idiopathic intracranial hypertension</td>
<td></td>
</tr>
<tr>
<td>Other neurological syndromes</td>
<td></td>
</tr>
<tr>
<td>Sensorineural hearing loss</td>
<td></td>
</tr>
<tr>
<td>Guillain–Barré syndrome</td>
<td></td>
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<tr>
<td>Transient global amnesia</td>
<td></td>
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<tr>
<td>Ocular syndromes</td>
<td></td>
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<tr>
<td>Dystonia–Parkinsonism</td>
<td></td>
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<tr>
<td>Cognitive dysfunction</td>
<td></td>
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<tr>
<td>Dementia</td>
<td></td>
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<tr>
<td>Other psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
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</tbody>
</table>
et al. [32] studied 24 patients with Sneddon’s syndrome. They found that the course of the disease in patients with high aCL levels was characterized by a more rapid progression and more severe clinical manifestations when compared with patients with normal aCL levels, suggesting their importance in the pathogenesis of some cases of Sneddon’s syndrome and the possible clinical value of aPL in identifying those at risk for severe clinical manifestations. Moreover, single photon emission computed tomography (SPECT) studies in patients with livedo reticularis without focal neurological deficits have shown deficits of cerebral perfusion, suggesting subclinical abnormalities and high risk of developing features of Sneddon’s syndrome [33].

**aPL and cerebral ischaemia in unselected patients**

A growing body of evidence supports an association between aPL and ischaemic stroke not only in SLE and/or APS but in unselected populations as well.

Studies on the prevalence of aPL in ischaemic stroke have been mainly focused on aCL rather than LA or both aCL and LA, accounting for the large variability in the results. Whilst most of the studies have found that aPL are associated with an increased risk in the incidence [34–39] and recurrence of cerebral ischaemia [40], other studies could not confirm the presence of these antibodies as an independent risk factor for cerebral ischaemia in the general population [41–44]. Table 2 summarizes available data.

In a very well designed study, Brey et al. [39] demonstrated an association between β2GPI-dependent aCL and incidence of ischaemic stroke and myocardial infarction. The study included a large cohort of men prospectively followed for 20 yr in the context of the Honolulu Heart Study. Their results showed that patients with IgG β2GPI-dependent aCL had a 2-fold increase in the odds of stroke within 15 yr of follow-up when compared with aCL-negative individuals. This study also gives further evidence for the role of aPL as an independent risk factor for ischaemic stroke in the general population.

In an attempt to find a more specific marker for ischaemic events, other aPL have also been evaluated. Tuhrim et al. [45] showed that antiphosphatidylserine antibodies were associated with increased risk for ischaemic stroke in a general stroke population when comparing 267 acute ischaemic stroke patients with 653 healthy controls. However, these findings still need to be confirmed owing to the lack of standardization of the antiphosphatidylserine antibodies assay and the lack of evidence on their pathogenic role.

In general, many factors may account for the discrepancies found between studies, mainly explained by the differences in the population selection and the variability in the duration of follow-up. In addition, many studies did not mention the confirmation of aCL and LA with repeated testing, although it is well known that aCL and LA can fluctuate over time. Some of the studies tested aPL within 48 h after the ischaemic event. It has been reported that aCL titres can decrease during the acute phase of the thrombotic event [46]. It is also well known that coagulation factors suffer different modifications during the acute phase of the thrombotic event. For this reason the presence of aPL should be confirmed at least from 1 to 3 months after the thrombotic event. Moreover, neither the aCL enzyme-linked immunosorbent assay (ELISA) test nor the selection of a cut-off value for a positive test has been fully standardized and variations among laboratories still remain of major concern.

**Recurrence ischaemic events in aPL-positive patients**

It is unclear whether the presence of aCL at the time of initial stroke increases the risk of recurrence in an unselected population. Levine et al. [47] examined in a prospective study 81 consecutive patients with aPL who developed focal cerebral ischaemia. The mean age of this cohort was younger than the average atherothrombembolic stroke victim and women were more commonly involved than men. The frequency of conventional stroke risk factors was lowest in the group of stroke patients with the highest levels of IgG aCL reactivity.

**Table 2. Relationship between antiphospholipid antibodies and ischaemic stroke in the general population**

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Patients (No.)</th>
<th>Population studied</th>
<th>aPL tested</th>
<th>aPL as independent risk factor for ischaemic stroke</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsburg/1992 [41]</td>
<td>100</td>
<td>Physician Health Study</td>
<td>aCL</td>
<td>No</td>
<td>Prospective</td>
</tr>
<tr>
<td>APASS/1993 [34]</td>
<td>255</td>
<td>Elderly</td>
<td>aCL</td>
<td>Yes</td>
<td>aCL tested in acute phase</td>
</tr>
<tr>
<td>Muir/1994 [42]</td>
<td>262</td>
<td>Young</td>
<td>aCL</td>
<td>No</td>
<td>aCL tested in acute phase</td>
</tr>
<tr>
<td>Metz/1998 [43]</td>
<td>151</td>
<td>Elderly</td>
<td>aCL, LA</td>
<td>No</td>
<td>LA screened by aPTT, no confirmatory tests performed</td>
</tr>
<tr>
<td>Zielinska/1999 [36]</td>
<td>194</td>
<td></td>
<td>aCL</td>
<td>Yes</td>
<td>aCL tested in acute phase</td>
</tr>
<tr>
<td>Tuhrim/1999 [37]</td>
<td>524</td>
<td>3 ethnic groups</td>
<td>aCL</td>
<td>Yes</td>
<td>aCL tested in acute phase</td>
</tr>
<tr>
<td>Kenet/2000 [38]</td>
<td>65</td>
<td>Children</td>
<td>aCL, LA</td>
<td>Yes</td>
<td>LA screened by aPTT, confirmed by DRVVT and KCT</td>
</tr>
<tr>
<td>Ahmed/2000 [44]</td>
<td>123</td>
<td>MONICA Study</td>
<td>aCL</td>
<td>No</td>
<td>Prospective</td>
</tr>
<tr>
<td>Brey/2001 [39]</td>
<td>259</td>
<td>Honolulu Heart Study</td>
<td>aCL</td>
<td>Yes</td>
<td>β2GPI-dependent aCL measured</td>
</tr>
</tbody>
</table>

All the studies were controlled. aPL: antiphospholipid antibodies; aCL: antcardiolipin antibodies; LA: lupus anticoagulant; β2GPI: β2-glycoprotein I; aPTT: activated partial thromboplastin time; DRVVT: diluted Russell’s viper venom time; KCT: kaolin clotting time.
Moreover, patients with highest IgG aCL had the shortest times to subsequent thrombo-occlusive events, mainly represented by cerebral infarction often occurring within the first year of follow-up, supporting that IgG aCL represented a risk factor for recurrent stroke. In a later study, the same authors [24] prospectively examined 132 consecutive patients with focal cerebral ischaemia harbouring aCL of at least 10 GPL units at the time of their index event. They found that the group of patients with aCL \(>40\) GPL was younger and had more prior strokes, more frequent subsequent thrombo-occlusive events and death, and a shorter median time to event when compared with patients with aCL \(<40\) GPL. The authors concluded that subsequent thrombo-occlusive events are associated with IgG aCL and death after focal cerebral ischaemia may occur sooner and more frequently in patients with aCL \(>40\) GPL, confirming the role of aCL as a risk factor for recurrent stroke.

These results were not confirmed by the Antiphospholipid Antibodies and Stroke Study (APASS) Group [40] in a study designed to examine whether the risk of subsequent thrombo-occlusive events or death was associated with an aCL titre \(>10\) GPL. First time ischaemic stroke patients were followed-up prospectively for a median time of 24 months for any thrombo-occlusive event or death. The authors showed that although a single aCL value \(>10\) GPL at the time of an initial stroke represented a significant independent risk factor for stroke, after adjusting for other stroke risk factors the aCL positivity did not confer a significantly increased risk for subsequent thrombo-occlusive events or deaths.

Another recent study of an elderly population did not find a higher incidence of recurrent stroke in patients positive for aCL \(>10\) GPL compared with negative patients [48].

The different follow-up and the fact that different levels of aCL are associated with a different thrombotic risk may account for the variability between these studies. Whilst Levine et al. [24] found an association between higher rates of recurrence and high levels of aCL \((>40\) GPL), the APASS study [40] included patients with low levels of aCL \((>10\) GPL) and therefore with a probable lower risk of thrombotic events. The study of Heinzl et al. [48] also included patients with low aCL levels. Moreover, the authors studied an elderly population with other cardiovascular risk factor exposure, which can minimize the impact of aCL in the development of recurrent stroke. In our experience the rate of recurrent thrombotic events is very high in aPL-positive patients who are not receiving anticoagulant therapy.

The practical significance of the association between elevated aCL titres and stroke with regard to patient management is not universally accepted. Recommendations that the best prophylactic regimen in these patients is high-intensity anticoagulation are based on retrospective analyses [49] and are probably most relevant to younger patients with evidence of prothrombotic tendencies and little risk of stroke. Our recommendation is that an evaluation for the presence of aPL, if not needed for all patients with cerebral ischaemia, requires special attention to be paid in assessing ischaemic episodes occurring in younger age groups, along with the search for prior APS- and SLE-related manifestations in the clinical history of these patients.

**Other less common cerebrovascular manifestations in aPL patients**

Acute ischaemic encephalopathy had been reported as an uncommon feature in SLE patients with aPL [50]. These patients can present acutely ill, confused, disoriented and obtunded with asymmetric quadriplegia, hyper-reflexia and bilateral plantar responses on examination. MRI often shows abnormalities and cerebral atrophy can be revealed.

Cerebral venous thrombosis (CVT) is another uncommon manifestation in APS. CVT may be encountered in a variety of hypercoagulable states [51], and had been reported more frequently in young women, often during pregnancy and the puerperium or associated with oral contraceptive pills [52]. There are only rare isolated reports of CVT in the presence of aPL [53–55], but it was Deschiens et al. [56] who postulated a role of aPL as a risk factor for CVT, possibly in association with other potential thrombophilia risk factors such as activated protein C resistance due to factor V Leiden mutation. Carhuapoma et al. [57] showed that onset of CVT occurs at a relatively young age and with relatively more extensive superficial and deep cerebral venous system involvement in patients with aPL than in those without.

**Epilepsy**

Early studies by Mackworth-Young and Hughes [58] found in 1985 a higher prevalence of aPL in SLE patients with seizures, higher than the accepted prevalence in the common SLE population. Later, Inzelberg and Korczyn [59] described four patients with late-onset seizures who did not have SLE but were positive for LA. These authors proposed that seizures in aPL-positive patients were the expression of ischaemic events occurring as a result of hypercoagulability. In fact, seizures are a well-known symptom of cerebral ischaemia [60]. These anecdotal reports were supported by further studies that statistically evaluated the association between epilepsy and aPL, mainly in patients affected by SLE.

Herranz et al. [61] confirmed that in SLE patients, moderate-to-high titres of IgG aCL are associated with seizures, suggesting their role in the aetiopathogenesis of epilepsy in SLE. These authors found a statistically significant high prevalence of aPL in SLE patients with seizures compared with control SLE patients. The titre and isotype of aCL were important in determining the presence of clinical complications. Moderate-to-high titres of IgG aCL were the most strongly implicated in relation to the appearance of seizures, while the IgM isotype appeared to be less specific. These findings provided evidence against a casual association and suggested that
the IgG isotype of aCL may have a pathogenic role in SLE-associated epilepsy.

Liou *et al.* [62] confirmed the association between aCL and epilepsy 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. They concluded that epilepsy may be a primary neuropsychiatric event associated with high titres of aCL antibodies in SLE patients.

Sabet *et al.* [63] determined the neurometabolic patterns of brain injury in SLE patients with APS. They found that epilepsy (and stroke) was more common in patients with SLE and aPL, suggesting that these antibodies increase thrombotic and non-thrombotic brain injuries.

Angelini *et al.* [64] studied 23 children with partial epileptic seizures and no clinical or serological evidence of SLE. None of them had MRI evidence of focal ischaemic lesions, but three of them, all with frontal lobe epilepsy, had aPL. These authors speculated that aPL could lead to immune-mediated damage, which could be a pathogenic mechanism for partial epilepsy.

However, the increased prevalence of autoantibodies, especially antinuclear antibodies (ANA) and aPL, in patients with epilepsy could also be attributed to the antiepileptic drugs and the origin and effects of these antibodies remain unclear [65].

Verrot *et al.* [66] studied 163 consecutive patients with epilepsy in order to determine the prevalence and the relationship between ANA and/or aCL with epilepsy in patients with no clinical signs of connective tissue disorders or APS. They found that aCL were present in 20% of the patients, independently of the type of epilepsy, the antiepileptic treatment or the age or sex of the patients. This study suggested a relationship between epilepsy and aCL, speculating that these antibodies can play a role in pathophysiology of epilepsy.

Peltola *et al.* [67] confirmed these results in a recent study designed to determine the effects of epilepsy and antiepileptic medications on the presence of ANA, anti-β2-GPI and aCL among patients with two well-defined chronic epileptic syndromes, as well as among patients with a new-onset untreated seizure disorder. The prevalence of aPL was shown to be greater in patients with epilepsy, including newly diagnosed seizure disorder. Newly diagnosed patients had a significantly greater prevalence of IgG aCL than the controls (21 vs 7%). The prevalence of IgG aCL was higher in patients with localization-related epilepsy than in those with generalized epilepsy (14 vs 8%). The prevalence of IgM aCL was significantly greater in all seizure groups (60% in localization-related epilepsy, 42% in generalized epilepsy, and 33% in newly diagnosed patients) compared with controls (7%). There was no association between autoantibodies and specific antiepileptic medications.

The authors concluded that the increased prevalence of autoantibodies found in patients with epilepsy, including those with newly diagnosed seizure disorders, was more strongly associated with epilepsy than with antiepileptic drugs, possibly indicating that an immune dysregulation is common in epilepsy.

There may be a primary immunological basis for seizures in some SLE patients with aPL owing to an aCL–brain phospholipid interaction [7]. aCL obtained from patients with SLE who had seizures have been shown to reduce a gamma-aminobutyric acid (GABA) receptor-mediated chloride current in snail neurons [68], suggesting the possibility that there is a direct and reversible mechanism through which aPL might lower the seizure threshold. Also, aPL have been demonstrated to bind directly to ependyma and myelin of fixed cat [69] and rat brain [70].

**Headache**

One of the most prominent features in patients with APS is headache. This symptom, a common complaint of APS patients in clinical practice, can vary from classic intermittent migraine to almost continuous incapacitating headache.

The association of migraine and aPL is controversial, with widely varying results from different series. Many authors have reported association with LA or aCL [71, 72], but others no association at all [73].

The difficulty in demonstrating a true association between aCL positivity and migraine stems in part from the high prevalence of migraine in the normal population and the relatively low prevalence of aCL positivity in otherwise healthy individuals. One of the major problems is also that headaches, often non-migrainous, have been loosely termed ‘migraine’, and these headaches may precede or accompany TIAs or CVA [74]. aPL have also been detected in patients with transient neurological symptoms including migraine aura. Therefore the controversy may be in part due to the inherent difficulty in distinguishing the transient focal neurological events of migraine from TIA.

The available data suggest an association between the migraine-like phenomena and aPL, but not between migraine headache and aPL. In 1988 Shuaib *et al.* [75] described migraine as an early prominent symptom in six patients with aPL, but Tietjen [76] pointed out that the role of these antibodies in the pathogenesis of migraine was poorly understood, calling for prospective, controlled studies to elucidate the actual role of aPL in migraine. Montalban *et al.* [77] carried out a prospective study in 103 consecutive patients with SLE, including a control group of 58 patients with migraine not associated with SLE. Although they found a high frequency of headache in SLE patients, they failed to find an association between the presence of aCL and migraine. No migraine control patients were found to have aCL. Tietjen *et al.* [78] assessed the frequency of aCL in migraine in a large prospective study that evaluated adult patients and normal controls under 60 years of age. The authors studied a group of 645 patients with transient focal neurological events, including 518 with migraine with aura, another group of 497 individuals with migraine without aura and 366 healthy controls.
The frequency of aCL did not differ significantly between groups. Verrotti et al. [79] studied the prevalence of aCL in children with migraine. In this study, 40 patients were divided into two groups according to the type of migraine: group I included 22 children suffering from migraine with and without aura; group II consisted of 18 children having migraine with prolonged aura or migrainous infarction, also called complicated migraine. Two groups of children were studied as controls: a group of 35 children with juvenile chronic arthritis and a group of 40 healthy sex- and age-matched children who did not suffer from migraine or any other neurological disease. No statistically significant differences were found in levels of aCL between group I and II and controls. The authors concluded that, in children with migraine, aCL are not more frequent than in healthy controls, suggesting that aCL are not implicated in the pathogenesis of migraine.

To date prospective studies using appropriate control groups failed to demonstrate association between aPL and migraine in SLE patients and higher prevalence of aPL in migraine sufferers.

In our experience, aPL, especially IgG aCL, are associated with the occurrence of chronic headache in SLE patients, but not with a particular subtype of headache or with migraine [80].

Anecdotal reports showed that anticoagulation treatment sometimes proved efficient in reducing the number and the intensity of headache attacks in selected APS patients [81].

Cuadrado et al. [82] recently reported five patients with APS and intractable headaches treated with a 7-day course of daily low-molecular-weight heparin. None had significant brain MRI lesions, but all had features of APS, notably previous venous thrombosis, livedo, previous recurrent pregnancy loss and thrombocytopenia. All of the five patients had a moderate-to-high titre aPL. In all five patients, there was a marked improvement (with a total disappearance in three) of the headache, in the majority within 48 h of starting heparin. The headache returned in all five patients on cessation of heparin treatment. The authors recognized that the decision to try anticoagulation treatment for an essentially non-thrombotic clinical feature is extremely difficult, but speculated that a possible future approach in aPL patients without major thrombosis and chronic intractable headache could be to treat with low-dose warfarin.

**Cognitive dysfunction**

Cognitive dysfunction varies from global dysfunction in the context of multi-infarct dementia to subtle cognitive deficits in otherwise asymptomatic patients with aPL. One of the most common complaints in these patients is of poor memory, difficulty in concentrating or difficulty in keeping their attention for a long time, indicating a probable preclinical phase of neurological involvement.

The recognition of subtle forms of cognitive dysfunction has been greatly facilitated by the application of formal neuropsychological assessment, mainly in patients with SLE. The relationship of cognitive dysfunction with aPL, detected by the presence of LA or aCL, had been investigated in cross-sectional [83, 84] and prospective/longitudinal studies [85, 86]. These studies showed that aPL may play a primary role in the pathogenesis of cognitive impairment and that the application of neuropsychological testing is useful in detecting an early neuropsychiatric involvement in patients with SLE.

A cross-sectional study of 70 patients with SLE [83] showed that delayed recognition memory performance was poorer in patients with elevated aCL levels. Denburg et al. [84] evaluated the relationship between aPL positivity (expressed as the LA) and cognitive dysfunction in patients with SLE in a cross-sectional study. LA-positive patients were 2 to 3 times more likely than LA-negative patients to be designated as cognitively impaired by the application of specific psychometric tests, with lower performance on tasks of verbal memory, cognitive flexibility and psychomotor speed. These deficits occurred independently of clinically overt neuropsychiatric manifestations. The authors speculated that LA positivity is associated with subclinical nervous system compromise, possibly on the basis of ongoing LA-related microthrombotic events or vasculopathy.

Menon et al. [86] determined the relationship between persistently raised aCL levels and neuropsychological performance in 45 patients with SLE. They found that levels of IgG aCL that were persistently elevated over a 2–3-yr period (as opposed to never or occasionally elevated) were associated with significantly poorer performance in cognitive function. Tasks requiring speed of attention and concentration appeared to be particularly affected in these patients.

Hanly et al. [85] analysed prospectively the association between changes in cognitive function and aCL over a period of 5 yr in SLE patients using standardized tests of cognitive function. Their results showed that patients with persistent IgG aCL positivity had a reduction in psychomotor speed, and patients with persistent IgA aCL positivity had a reduction in conceptual reasoning and executive ability, suggesting that IgG and IgA aCL may be responsible for long-term subtle deterioration in cognitive function in patients with SLE. An important finding of this study was that the observed changes in cognitive performance were not associated with persistent elevation of the level of anti-dsDNA antibodies, showing that they can occur independently of generalized SLE disease activity and supporting the hypothesis that aPL play a primary role in the aetiology of these manifestations.

Clinical implications of these findings are that, although the current evidence does not support the introduction of aggressive anticoagulation as a strategy to prevent subclinical cognitive impairment, there may be a role for more benign therapies such as low-dose aspirin or antimalarials. On the other hand, anecdotal reports of improvement of these symptoms after anticoagulation therapy commenced for other reasons in APS patients may provide some support for the theory that arterial
thrombosis and/or ischaemia represent the primary cause of this type of central nervous system dysfunction, supporting the utility of further longitudinal case-control trials to answer the question of whether an anticoagulation treatment with low targeted international normalized ratio (INR) could be superior to aspirin in these patients.

Long-term prospective studies are also required to determine if the risk of cognitive impairment in patients with persistently elevated aPL levels is cumulative over time. If this is confirmed, the next step will be to identify effective therapies with an acceptable benefit/toxicity ratio.

Dementia

A chronic multifocal disease, defined as a recurrent or progressive neurological deterioration attributable to cerebrovascular disease, can produce multi-infarct dementia. Our group [5] first described this manifestation in 1987. We went on to describe in 1989 [21] the clinical and serological features of 35 patients with aPL and cerebrovascular disease. Strokes were often multiple and were followed by multi-infarct dementia in nine patients. This dementia, generally associated with a loss of cognitive functions and impairment of skills, poor concentration, memory dysfunction, language impairment and judgemental defects, does not present with peculiar characteristics. It can not be differentiated from other kinds of dementia such as in Alzheimer’s disease, senile dementia or metabolic/vascular conditions involving the brain. Many other authors have since reported this complication in patients with recurrent strokes [23, 87, 88].

Westermann et al. [89] described brain biopsy findings from a patient with multi-infarct dementia and APS. Microscopic examination showed luminal occlusion by thrombi, and marked endothelial hyperplasia of small meningeal and cortical arterioles, suggesting that the pathogenesis of this cerebral vasculopathy is non-inflammatory and is associated with reactive endothelial hyperplasia and thrombosis of small arterioles. Hilkert et al. [19] reported on a 55-year-old man suffering from progressive dementia and PAPS, in whom cerebral glucose metabolism and blood flow were examined by positron emission tomography (PET). Cerebral atrophy and a moderate number of white matter hyperintensities were detected on MRI, whereas the PET scans showed a considerable diffuse impairment of cortical glucose metabolism combined with a reduced cerebral perfusion in the arterial border zones. These findings indicate that PAPS-associated vascular dementia is accompanied by a cortical neuronal loss, presumably caused by a small-vessel disease with immune-mediated intravascular thrombosis. Mosek et al. [90] examined the relationship of aPL to dementia in the elderly in a case-control study. They found that five of the 87 demented patients (6%), but none of the 69 controls, had significantly elevated aCL IgG levels (above 20 GPL). All the patients with high aCL IgG levels were diagnosed clinically as having dementia of the Alzheimer type, except for one who had mixed dementia, and none had features of an immune-mediated disease. This study showed a small but significant number of patients with dementia having high levels of aPL. The role of the aPL in these patients, with apparently diffuse brain disease, is currently unknown.

Other psychiatric disorders

Although depression and psychosis have been associated with aPL, it had been postulated that autoantibodies, and specifically aPL, may represent an adverse response to neuroleptic treatment. It is also difficult to establish whether or not the psychiatric symptoms are due to a psychological reaction of suffering from a chronic disorder. In addition, corticosteroid therapy, mainly used in secondary APS patients, may itself produce psychiatric symptoms.

Schwartz et al. [91] studied 34 unmedicated patients without known autoimmune disorders admitted with acute psychosis. aCL and LA were determined before and after neuroleptic treatment to evaluate the presence of antibodies relative to the treatment condition. They found that 32% of the unmedicated psychotic patients had aPL. Elevated titres of IgG aCL isotype were detected in 24% of unmedicated patients, and 9% had LA, neither of which was present in 20 normal control subjects.

Of the 22 patients followed up after medication, 31.8% showed moderate titres of IgG aCL, and 18.2% LA positivity. There was no relationship between the presence of aCL or LA and type of neuroleptic used. This study showed an increased incidence of LA and aCL in untreated psychotic patients and that the presence of these antibodies cannot be simply assumed as a result of the treatment. Therefore aPL may be primarily associated with psychosis.

Chorea

A strong relationship between aPL and chorea had been reported in retrospective studies. Chorea is a rare manifestation of SLE, occurring in 1–3% of all SLE patients. This type of movement disorder has been documented in pregnancy and as a complication of oral contraceptives [92]. Its association with LA alone [93], or more commonly with SLE, has been infrequently reported [94]. It seems that chorea is more frequent in patients with PAPS than in those with SLE.

Because chorea in SLE is often unilateral, acute in onset and is often followed by other CNS manifestations, a vascular pathogenesis is probable in these patients. A similar mechanism may also be present in patients who demonstrate the disorder subsequent to taking oral contraceptives. It is also possible that increased dopaminergic activity within the corpus striatum, a mechanism postulated to occur particularly in patients taking compounds such as d-amphetamine and levodopa, may also play some role [95].

It has been postulated that aPL can cause chorea by an antigen/antibodies mechanism binding phospholipid in the basal ganglia [96].
Cervera et al. [97] reviewed the clinical, radiological and immunological characteristics of 50 patients with chorea and APS. Fifty-eight per cent of patients had defined SLE, 12% ‘lupus-like’ syndrome and 30% PAPS. Twelve per cent of patients developed chorea soon after they started taking oestrogen-containing oral contraceptives, 6% developed chorea gravidarum and 2% developed chorea shortly after delivery. Most patients (66%) had only one episode of chorea. Chorea was bilateral in 55% of patients. Computed tomography and MRI scans reported cerebral infarcts in 35% of patients. The chorea in these patients responded to a variety of medications, for example steroids, haloperidol, antiaggregants, anticoagulants or a combination of therapy, usually prescribed in the presence of other manifestations of APS or SLE. Many patients responded well to haloperidol and to the discontinuation of oral contraception if this was the precipitating factor.

Multiple sclerosis

Clinical syndromes mimicking multiple sclerosis (MS), mainly in its relapsing–remitting pattern, are reported to occur in association with aPL [30]. In 1994, Scott et al. [98] reported four patients presenting with multiple neurological manifestations, including vertigo, aphasia, unilateral visual loss, diplopia or hemiparesis, in different combinations over several years, with variable degrees of recovery after the episodes. All had white-matter lesions and all had received the clinical diagnosis of MS. IgG aCL were positive at medium to high levels in the four patients, and LA was also found in three of them. In addition, all but one patient had previous clinical manifestations suggestive of APS, such as venous thrombosis, recurrent miscarriages and thrombocytopenia.

More recent studies showed a controversial relationship between MS diagnosis and the presence of aPL. Tourbah et al. [99] found that patients with MS with autoimmune features, including those with titres of ANA of 1:100 or less and/or aPL, were not different from others with MS regarding age of onset, presenting symptoms and signs, neurological examination findings or disease course. The authors found that patients with an MS-like illness and aPL were so similar to patients with MS that in their opinion they should not be excluded from clinical trials.

In 1998 Karussis et al. [100] screened a population of 70 classic and 100 non-classic MS patients, labelling as non-classic those with features unusual for MS. They found a strikingly significant proportion of aCL-positive patients in the non-classic MS group. Most of the positive patients in the non-classic MS group had a similar clinical manifestation pattern, such as progressive myelopathy, spinocerebellar syndrome or neuromyelitis optica. They concluded that a clinical subset of patients with probable or definite diagnosis of MS but with consistently elevated levels of aCL show a slower progression and some atypical features for MS, such as persistent headaches and absence of oligoclonal bands in the cerebrospinal fluid. Therefore in patients with MS showing such clinical features, aCL testing is recommended. They speculated that these antibodies may be involved in the pathogenesis of the neurological symptoms, and therefore, management should include antiplatelet or even anticoagulant agents.

Recently Cuadrado et al. [30] analysed the clinical, laboratory and imaging findings of MS-like expression in a cohort of patients with APS in an attempt to identify parameters that might differentiate the two entities. These authors studied 27 patients with a previous diagnosis of probable or definite MS made by a neurologist, all of them referred because of symptoms suggesting an underlying connective tissue disease, uncommon findings for MS on MRI, atypical evolution of MS or aPL positivity. MRI was performed in every patient and compared with MRI of 25 definite MS patients who did not have aPL. In the past medical history, eight patients with PAPS and six with APS secondary to SLE had had symptoms related to these conditions. Neurological symptoms and the results of physical examination of the patients were not different from those common in MS patients. Laboratory findings and MRI studies were not useful tools to distinguish APS from MS. Most of the patients with PAPS showed a good response to oral anticoagulant treatment. In patients with secondary APS, the outcome was poorer. The authors concluded that APS and MS can be difficult to distinguish. A careful medical history, a previous history of thrombosis and/or fetal loss, and the response to anticoagulant therapy might be helpful in the differential diagnosis. They recommended testing for aPL in all patients with MS.

Roussel et al. [101] studied the prevalence of serum aPL, aCL and anti-β2-GPI, in 89 patients affected with possible, probable or definite MS and no clinical evidence of associated autoimmune disorder. About one-third of the patients had aPL, either aCL, anti-β2-GPI or both. Because of the known high frequency of aCL in ischaemic stroke they also studied sera from a series of such patients, and the frequency of both aCL and anti-β2-GPI was higher in MS than in ischaemic stroke. No correlation was found between aPL and the category of MS, its clinical course or clinical symptoms, nor atypical lesions by MRI. They concluded that aCL and anti-β2-GPI are neither rare in MS nor associated with a specific clinical form of the disease and therefore they cannot be used as a diagnosis exclusion criteria.

Sastre-Garriga et al. [102] recently studied 296 randomly selected patients with MS and 51 healthy controls; aCL, anti-β2-GPI or antiprothrombin were found in six patients. No predominance of any kind of clinical manifestation and no cardinal manifestation of PAPS were found in these patients. They concluded that aCL tests should be performed only when a suspicion of APS is raised and atypical clinical presentation for MS is found, but not in unselected cases.

In this case the different results can be justified on the basis of different population selection criteria and differences in laboratory techniques.

We believe that some APS patients can be misdiagnosed as having MS, making this a crucial point for
the therapeutic approach. A careful interview of the patient, a past medical history of thrombotic events and pregnancy morbidity in female patients may be useful in the differential diagnosis, favouring APS. The abruptness of onset and resolution of symptoms, especially in regard to visual symptoms (i.e. amaurosis fugax), and atypical neurological features for MS such as headache or epilepsy strongly suggest APS rather than MS. We think that if not all, at least a subgroup of patients with ‘non-classic’ MS should be tested for aPL.

Transverse myelitis

Harris et al. [3] described in 1985 the case of a 45-yr-old woman who developed transverse myelitis in the context of a lupus-like illness. Antibodies to cardiolipin of the IgM class were detected in high titres in the serum. The authors speculated that these aCL may have played a part in the pathogenesis of this peculiar neurological manifestation in this patient.

Subsequently, many other authors confirmed the association between aPL and transverse myelitis. The prevalence of aPL had been shown to be higher in SLE patients with transverse myelitis compared with SLE patients in general [73].

Lavalle et al. [103] reported 10 of 12 patients with transverse myelitis and SLE as having aCL, and the other two evidence of venereal disease research laboratory (VDRL) positivity and prolonged activated partial thromboplastin time (aPTT). Both IgG and IgM isotype aCL were detected in 8/10 patients. The authors concluded that there is a strong association between transverse myelitis in SLE and the presence of aPL.

Ruiz-Arguelles et al. [104] described a patient with refractory hiccup as the heralding symptom of transverse myelitis in association with aCL.

The pathophysiology of spinal cord damage in aPL-associated myelopathy is uncertain; however both ischaemia and antibody-mediated interaction have been postulated.

Kovacs et al. [105] evaluated 14 patients with SLE and transverse myelitis and 91 additional cases published in the literature. Forty-three per cent of their patients and 64% of the patients reported in the literature were aPL positive, confirming the strong association of transverse myelitis with aPL.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension, also known as pseudotumour cerebri, is the term used to describe the occurrence of raised intracranial pressure that is not due to mass lesions, obstruction of cerebrospinal fluid flow or focal structural abnormalities in alert and oriented patients. The term idiopathic requires the exclusion of intracranial venous sinus thrombosis.

Idiopathic intracranial hypertension is frequently associated with aCL and can be the presenting symptom of APS. The association of idiopathic intracranial hypertension with aPL has been acknowledged only recently [106]. However, its true incidence is still unknown. Sussman et al. [107] reported on 11 out of 38 patients (29%) with aPL and idiopathic intracranial hypertension. However, only four had aCL without other prothrombotic risk factors or evidence of sinus thrombosis.

Leker et al. [108] found aCL in six out of 14 patients (43%) with idiopathic intracranial hypertension. They did not find differences in clinical, laboratory or radiological findings that distinguished between patients with idiopathic intracranial hypertension with and without aCL.

Kesler et al. [109], in a retrospective study, confirmed the association between idiopathic intracranial hypertension and aCL, although they found a lower frequency of aCL in their patients. Three out of 37 patients (8.1%) were shown to be aCL positive, with a prevalence lower than that reported in the two previously published studies.

Sensorineural hearing loss

A link between sensorineural hearing loss and autoimmune disease has been postulated by many authors who described the association of sensorineural hearing loss with aPL in several reports [110–112].

Hisashi et al. [110] described the occurrence of sensorineural hearing loss in a young woman diagnosed with SLE. Serological tests for syphilis were false-positive and IgG aCL were positive. The authors postulated the association of sudden profound sensorineural hearing loss with aCL in patients with autoimmune diseases.

Casoli and Tumiati [111] described a 55-yr-old woman with a 6-year history of Sjögren’s syndrome who presented with IgG and IgM aCL and developed a sudden onset of sensorineural hearing loss associated with vertigo.

Toubi et al. [113] studied 30 patients, 11 suffering from sudden deafness and 19 from progressive sensorineural hearing loss, and 20 matched healthy controls. They found that 27% of patients had low to moderate titres of aCL, while none of the control group presented with aCL. The authors concluded that aCL may play an important role in the pathogenesis of this disability, speculating about the possibility of anticoagulant therapy for these patients.

Naarendorp et al. [114] described six patients with SLE or a lupus-like syndrome, who developed sudden sensorineural hearing loss and had elevated serum levels of aCL or LA. They concluded that acute onset of sensorineural hearing loss in the presence of aCL may be a manifestation of APS, and that anticoagulation treatment was to be recommended for these patients.

Guillain–Barré syndrome

Guillain–Barré syndrome is a transient neurological disorder characterized by an inflammatory demyelination of peripheral nerves. Although the pathogenesis of this disorder has not been elucidated, there is increasing evidence pointing to an autoimmune aetiology. This demyelinating neuropathy, also uncommon in SLE
patients, was associated with aPL in the original descriptions of the Hughes syndrome [4].

Gilbard et al. [115] studied the reactivity of Guillain–Barré syndrome sera with various phospholipids that are known to be important constituents of myelin, and serve as autoantigens in other autoimmune conditions, demonstrating that some Guillain–Barré syndrome patients produce autoantibodies to various phospholipid and nuclear antigens. However, these autoantibodies are probably produced as a result of the myelin damage rather than being the cause of the demyelination.

Transient global amnesia

Transient global amnesia, a syndrome of sudden unexplained short-term memory loss in association with aPL was reported by Montalban et al. [116]. Some regard this disturbance as migrainous in origin, but other mechanisms such as epileptic seizure have been advocated as involved in its pathogenesis [117].

Ocular syndromes

Ocular vaso-occlusive disease is frequently found in patients with APS [118]. Amaurosis fugax is one of the most common manifestations. Optic neuropathy is a well-known ocular manifestation occurring in patients with SLE, and it remains one of the major causes of blindness in these patients. Bilateral optic neuropathy in SLE occurs more frequently than monolateral optic neuropathy, and the associated main neurological manifestation seen in these patients is transverse myelitis [119, 120], particularly in SLE patients with bilateral optic nerve disease (Devic’s syndrome).

On the other hand, optic neuropathy is less frequently described in APS patients without SLE [121] and tends to be unilateral in these cases. Giorgi et al. [122] reported on six SLE patients with optic neuropathy, one of whom was considered to have APS. This patient had monolateral optic neuropathy, whereas the other five SLE patients had bilateral optic nerve disease. These authors considered the monolateral occurrence of optic neuropathy as a focal neurological disease due to a thrombotic event involving the ciliary vasculature. Conversely, bilateral optic nerve damage in SLE was considered to be due to different immunological mechanisms, such as vasculitis.

Dystonia–Parkinsonism

Although basal ganglia involvement is often confirmed on MRI, extrapyramidal disorders such as Parkinsonism and dystonia are unusual in APS.

Milanov and Bogdanova [123] recently reported on a 60-yr-old man diagnosed as having PAPS who presented with bradykinesia and stiffness of his right hand. Neurological examination revealed constant, marked dystonic posturing, rigidity and bradykinesia of the right hand in the presence of IgM aCL, while IgG aCL was negative. MRI of the brain showed several hyperintense lesions in the basal ganglia and in the periventricular white matter and diffuse hyperintensity of the subcortical white matter bilaterally in the parietal regions. No clinical improvement was achieved by levodopa, dopamine agonists or anticholinergics.

The authors concluded that dystonia and Parkinsonism may be associated with APS as well as other movement disorders.

Conclusion

The description of APS [1] brought important insights in the understanding of pathogenetic mechanisms of CNS manifestations in autoimmune diseases and a fundamental change in medical practice. The recognition that some individuals should be treated with anticoagulation rather than steroids or immunosuppressive drugs has changed the outcome of a substantial number of patients.

In a previous paper from our group we found that CNS disease in SLE was significantly associated with the presence of aPL [124]. A very comprehensive review on CNS syndromes in SLE has been published recently [125]. Cerebral ischaemia due to vessel occlusion is considered the most important cause of CNS disease in SLE and aPL play a prominent role in this process [126].

Our more recent experience confirmed a strong association between the presence of aPL and cerebrovascular disease, headache, cognitive dysfunction and seizures in a large series of SLE patients [127] supporting the theory that an occlusive vasculopathy may be a major mechanism for neuropsychiatric lupus.

Taking into account the available data we recommend testing for aPL not only for patients with autoimmune diseases and neuropsychiatric manifestations but also individuals without an underlying autoimmune disease who develop ischaemic cerebral events, especially when the patients are under 40 yr, and those with ‘non-classic’ MS clinical features, transverse myelitis and atypical seizures. Individuals with multiple hyperintensity lesions at brain MRI without other known causes, especially when under 40 yr, should also be tested for aPL.

It is our current practice to anticoagulate patients with aPL suffering from cerebral ischaemia with a target INR ≥ 3.0 in order to prevent recurrences. Our recommendation once the patient has had a proven thrombosis associated with aPL is long-term (possibly life-long) warfarin therapy. Discontinuation of warfarin can lead to major recurrent thrombosis. Low-dose aspirin alone does not prevent recurrent thrombosis in these patients [49]. Oral anticoagulation carries an inevitable risk of serious haemorrhage. In our experience the risk of fatal bleeding in patients with APS and previous thrombosis treated with oral anticoagulation to a target INR of 3.5 was similar to that in groups of patients treated to lower target ratios [128].

The role of steroids and immunosuppressive drugs in the treatment of patients with aPL and thrombosis is uncertain. Their use is probably justified only in patients with life-threatening conditions with repeated episodes of thrombosis despite adequate anticoagulation treatment.
To date no study has addressed the prophylactic management of aPL-positive individuals without previous thrombosis. A prospective randomized trial comparing low-dose aspirin with low-intensity warfarin in patients with SLE and/or adverse pregnancy history is currently in progress in the UK. Until these data are available we recommend low-dose aspirin (75 mg/day) indefinitely in the thromboprophylaxis of aPL-positive subjects without previous thrombosis. Table 3 summarizes our recommendations on the thromboprophylaxis of aPL-positive individuals.

Perhaps the association between aPL and neuro-psychiatric manifestations different from cerebrovascular disease—such as headache and seizures—warrants the consideration of anticoagulation treatment at least in those patients with more severe manifestations and an unsatisfactory response to traditional treatments for headache or conventional anti-epileptic drugs. Recent anecdotal reports from our group described a dramatic clinical improvement in patients with APS and chronic headache not responsive to conventional treatment after commencing oral anticoagulation or heparin to prevent recurrences of thrombosis [82, 129].

A clinical trial comparing low-molecular-weight heparin with placebo in patients with aPL and chronic incapacitating headache is currently in progress in our unit [130].

Table 3. Thromboprophylaxis of aPL-positive individuals: recommendations

<table>
<thead>
<tr>
<th>Asymptomatic subjects:</th>
<th>Low-dose aspirin</th>
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<tbody>
<tr>
<td>Thrombosis:</td>
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<td>Long-term warfarin</td>
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<td>Venous: INR 2.5–3.0</td>
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<tr>
<td>Arterial: INR &gt; 3.0</td>
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<tr>
<td>Recurrent thrombosis:</td>
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<tr>
<td>Warfarin INR &gt; 3.0+low-dose aspirin</td>
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<tr>
<td>Resistant cases with recurrent thrombosis:</td>
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<tr>
<td>Warfarin &gt; 3.0+</td>
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<td>Immunosuppressive drugs</td>
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<td>Corticosteroids</td>
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<td>Plasmapheresis</td>
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References

CNS involvement in the antiphospholipid syndrome


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