Antiphospholipid syndrome and central nervous system

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Classification criteria, etiology, pathogenesis, major central nervous system (CNS) manifestations of the antiphospholipid syndrome (APS), as well as diagnostic and therapeutic approach are discussed in the article, supported by several MRI findings to illustrate differential complexity of selected topics. Close interplay of inflammation, autoimmunity, coagulation cascade, vasculature bed, neuron physiology and demyelinization in APS is elaborated. Cerebrovascular disease, multiple sclerosis-like syndrome, seizures, cognitive dysfunction, headache and migraine, chorea and catastrophic antiphospholipid syndrome (CAPS) are discussed as the most prominent CNS manifestations of the APS.

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1. Introduction

The antiphospholipid (Hughes) syndrome was first described in 1983. It is the autoimmune condition defined by thrombosis (arterial or venous) and/or pregnancy morbidity (most often recurrent spontaneous abortions) associated with persistently positive antiphospholipid antibodies (aPL), namely anticardiolipin antibodies (aCL), lupus anticoagulant (LA) and/or β2 glycoprotein I (β2GPI) [1–4]. In addition to peripheral arterial and venous thrombosis affecting any size of vessels, a variety of clinical manifestations is reported: skin disease, cardiac, pulmonary and renal involvement, haematologic manifestations and wide spectrum of neurological disorders. Early and late fetal losses, premature births and preeclampsia are the most frequent obstetric manifestations. In the absence of underlying connective tissue disorder, the syndrome is defined as primary APS, whereas secondary APS is seen in patients with other connective tissue diseases, most often systemic lupus erythematosus (SLE) [1,5,8].

1.1. Classification criteria

Classification of APS is complex in nature. The variability of clinical presentation and the insufficient sensitivity and/or specificity of the available laboratory tests as well as the selection bias of different populations screened, has influenced development of classification criteria for APS. Today most experts use 2006 Revised Classification criteria based on the preliminary international (Sapporo 1999) criteria for definite APS [7]. APS is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met.

1.1.1. Clinical criteria

1. Vascular thrombosis—one or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity: (a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus or (b) one or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency or (c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.
1.1.2. Laboratory criteria

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).

2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e., >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.

3. Anti-β2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

1.2. Etiology and pathogenesis of APS

APS has been originally described in the subset of SLE patients having recurrent thrombotic events, and only later described in patients with no underlying systemic disease [8]. Two diseases show important similarities regarding etiology, pathogenesis, and clinical manifestations. Genetic and environmental factors are involved in the etiology of APS. Association with different HLA loci has been demonstrated throughout different patient populations [9]. Infections, autoimmune and other inflammatory diseases, drugs, and neoplasms might induce aPL. Abnormal exposure of phosphatidylserine during apoptosis might be the link between autoimmune and malignant diseases and APS. The pathogenesis of APS involves all components of the immune system. However, the most prominent and central role is the one of aPL because of the close association with the predominant clinical features of venous and arterial thrombosis. aPL autoantibodies originally named LA, are directed against a wide variety of phospholipid-binding proteins (cofactors). β2GPI is the main target of aPL. It seems that only high affinity anti-β2GPI antibodies have pathogenic role in APS [10]. β2GPI has no known physiological function. It avidly binds to negatively charged phospholipids (e.g. cardiolipin, phosphatidylserine and phosphatidylinositol), thus exposing epitope to which anti-β2GPI antibodies bind, activating the protein. Complex β2GPI–anti-β2GPI–phospholipid interacts with different cells and haemostatic reactions [11]. These interactions can be divided into four groups: activation of endothelial cells, monocytes and platelets, complement activation, interference with coagulation and fibrinolysis and proatherosclerotic effects [12]. Toll like receptors 4 (TLR4) and annexin 2 play major role in endothelial activation and expression of prothrombotic and proinflammatory phenotype. TLR4 and interleukin 1 receptors may be important in monocyte activation and consequent upregulation of tissue factor involving different intracellular signal pathways [13,14]. Platelets activation with β2GPI-antibody complex is mediated at least by two receptors: LDL receptor related protein 8 (LRL-8) and the platelet adhesive receptor glycoprotein Iba (GPIb α) [15]. The aPL effect on haemostatic mechanisms is very complex, resulting in protein C resistance, inhibition of protein S, antithrombin and tissue factor pathway inhibition. aPL also impair fibrinolysis by inhibiting tPA, interacting with antiplasmin and activating factor XI [16,17]. Role of activated complement system in the coagulation and inflammation induced by aPL is very important. Components of activated complement system like C3a and C5a activate monocytes and macrophages, increase production of tissue factor, activating endothelial cells, trigger inflammation process and inflict some direct damage through membrane attack complex [18–20]. Causal relationship between β2GPI and atherosclerosis remains speculative, since clinical studies did not confirm hypothesis that β2GPI-antibody acts proatherogenic through endothelial perturbation and crossreactivity with oxidized low-density lipoproteins [21,22]. Small detached membrane buds called microparticles, released during cell apoptosis, are found to be more abundant in patients with LA, particularly those with thrombotic complications. Since they are very rich in phospholipids, microparticles might lead to thrombin formation and thrombosis. Results from different studies are controversial, and so is the role of microparticles [23,24]. Prothrombotic effects of aPL in the CNS are consistent with previously described pathogenesis. The specific role of aPL in nonthrombotic CNS manifestations of APS is less clear. Cognitive dysfunction or demyelination might be related to aPL–cellular interactions. Disrupted blood–brain barrier or intrathecal synthesis of aPL might be responsible [25]. Astrocyte proliferation and the nonspecific permeabilization and depolarization of synaptoneurosomes induced by aPL were found experimentally [26]. The exact etiologic role of aPL in APS–associated transverse myelitis remains to be established. A direct interaction between aPL and cellular elements of the CNS, rather than aPL-associated thrombosis, seems to be a more plausible mechanism. Patients with an APS–related transverse myelitis, especially those with the recurrent episodes, may have an unrecognized myelin-specific antibody [12].

1.3. Imaging of APS

The spectrum of radiologic and neuroradiologic findings in patients with APS is largely consequence of multiple arterial or venous thromboses. Infarcts of various sizes and focal hyperintense lesions of white matter are the most common abnormalities seen on CT and MR imaging in patients with APS [27,28].

MRI findings in APS can be similar to those seen in multiple sclerosis (MS), SLE, Sjögren syndrome, Adamantinoides-Behcet disease, sarcoidosis and cerebrovascular disease [29]. Diagnostic criteria were developed to increase the specificity of cerebral and spinal MRI for demyelination in rheumatic diseases [29,30]. MRI criteria are based on size, number, contrast enhancement and location of focal hyperintensity on T2 or FLAIR images. Patients with APS are found to have small focal diffuse hyperintensity lesions on T2 images in subcortical white matter. Furthermore, MRI lesions seen in association with APS are usually static on repeated MRI [6].

2. Central nervous system involvement in APS

Cerebral involvement in APS is common, characterized by different clinical manifestations, which may be the presenting features or may appear in the course of disease. The reported manifestations are cerebral ischemic events, epilepsy, dementia, cognitive deficits, headaches, psychiatric disorders, chorea, MS-like disease, transverse myelitis, and ocular symptoms. Presence of APL in patients without criteria for APS may also be associated with neuropsychiatric and cognitive disturbances. Neurological disorders may result from vascular thrombotic events or direct injury to neuronal tissue [4,31].

2.1. Cerebrovascular disease

Strokes and transient ischemic attack (TIA) are the most common arterial thrombotic event in patients with APS, stroke being the most serious complication causing significant morbidity [31–34]. An ischemic stroke can present as a single episode, but it may reappear. Patients with aPL are usually younger and more often women in comparison with stroke patients who are aPL negative [35]. In almost 20% of stroke patients under 45 years, the stroke may be associated with APS [36] and aPL are found at overall prevalence of 6.8% in stroke patients [37]. Krause and group have shown significant association between valvular heart disease (possible source for emboli causing ischemic
A 50 years old woman, with a history of recurrent pregnancy loss, and one preterm birth, Raynaud phenomenon, nonerosive arthritis and photosensitivity, presented with fatigue, malaise, weight loss, headaches, heart murmur, very discrete left sided hemiparesis and mild depression. She had high levels of anti-DNA, anti-histone and aCl IgM and IgG. LA was positive. A diagnosis of SLE with secondary APS was established. T2-weighted MR images in axial plane and T2 images in frontal plane show multiple, predominantly subcortically distributed, white matter lesions. MR signal characteristics and distribution of lesions are not typical for MS.

Some published studies have demonstrated the association between β2GPI-dependent aCL and the incidence of ischemic strokes and myocardial infarction [39]. There were several studies investigating the association of increased stroke rate and the APS in general population—the results are controversial. In Euro-Phospholipid Project Group study that encompassed 1000 patients with APS, and observed them during their lives, 712 neurological manifestations occurred during patients lives and almost 400 events were related to cerebrovascular cause [5]. There are also controversial results in studies investigating association of presence of aPL at the time of initial stroke and increased risk of recurrence in general population.

Recent literature review showed that aCL is strong risk factor in case when IgG isotype and medium/high titers were considered, but also that LA is risk factor for both venous and arterial thrombosis [40]. Sanna and colleagues have found strong association of aPL and cerebrovascular disease (stroke and TIAs) in a study that analyzed association of APS and cerebrovascular disease in SLE patients. They have found cerebrovascular disease in 14.5% of 323 consecutive SLE patients [41]. See Fig. 1 showing white matter lesions on MRI in one of our patients with SLE and secondary APS, transient leftsided hemiparesis, depression and cognitive impairment.

Sneddon’s syndrome is a progressive neurological disorder of unknown etiology which combines cerebrovascular disease and livedo reticularis. Most affected arteries in Sneddon’s syndrome are small and medium sized arteries of skin and brain [42]. Predominant pathology is noninflammatory occlusive arteriopathy [43]. The prevalence of aPL of 41% was found in patients diagnosed with Sneddon’s syndrome [44].

There are also some less common cerebral thrombotic diseases possibly associated with APS—acute ischemic encephalopathy and moyamoya disease. Acute ischemic encephalopathy is rare feature of SLE patients with aPLs, presented in only 1.1% of patients in Euro-Phospholipid Project Group study [5]. Patients with acute ischemic encephalopathy present acutely ill, confused, disoriented, having hyperreflexia, asymmetrical quadriaparesis and bilateral extensor responses [45]. There are only few cases of moyamoya disease, rare disorder characterised with progressive vascular stenosis, that are associated with aPL [46]. The only cases of moyamoya disease associated with aPL were described in children [47].

2.2. Multiple sclerosis-like syndrome

Some manifestations reported in patients with APS can mimic MS: myelitis, balance and sensory problems may occur in association with aPL, thus leading to the mistaken diagnosis of MS. Analyzing 27 patients with APS in whom the diagnosis of MS was established, Cuadrado described that neurologic symptoms and physical examination of the patients were not different from those seen in MS patients. It seems that nearly one-third of aPL positive
Fig. 2. A 38 years old female presented 18 years ago with vestibular neuronitis, followed by migratory arthralgias and missed abortion, increased levels of ANA, anti-DNA, aPL and capillaroscopy finding showing SLE pattern. SLE with secondary APS was diagnosed. Four years later she developed typical MS, fulfilling the MS criteria including the CSF finding revealing the intrathecal synthesis of IgG. Recent brain MRI shows multiple confluent periventricular lesions on axial FLAIR images. On sagittal FLAIR images there is clear radial orientation of lesions, predominantly in the corpus callosum. Also there are small multiple lesions in subcortical white matter. Multiple focal lesions are also visible on sagittal T2 images of cervical spinal cord. Brain images and spinal cord images met all MS criteria.

patients were sometimes at any stage of their disease evaluated of having MS [4,31,48]. The number of patients diagnosed with MS, later shown to have APS has grown, but the true prevalence of aPL in unselected MS populations is controversial. Although only stroke and TIA are included in the classification criteria, more complex neurological manifestations are being recognized and multifocal white matter lesions on brain MRI are common [6]. In patients clinically diagnosed with MS the high levels of aPL may be found, while in patients clinically diagnosed with SLE and/or APS the MRI studies may reveal the subcortical white matter lesions. Furthermore, in some patients with APS having sensory or motor dysfunction, optic neuritis or transverse myelitis, the MRI studies can show multiple T2 hyperintense brain lesions, which may not be easy to differentiate from MS. Some authors suggest that lesions associated with APS, found on repeated MRI studies are usually static compared with the more dynamic lesions seen in MS. It is also suggested that magnetization transfer imaging combined with standard MRI can differentiate MS from APS. Morphology of the lesions is also important, elongated ovoid shaped lesions (Dawsons fingers) and “black holes” are more characteristic of MS. Lesion distribution can also be helpful, since subcortical lesions predominate in APS and periventricular, especially corpus callosum lesions are more common in MS [49]. Although transverse myelitis and autoimmune optic neuritis are rare manifestations of primary or secondary APS reported in 0.4 and 1% of patients respectively, it is recommended that SLE and secondary APS must be suspected in patients with those conditions [6,50,29,51]. MS, primary APS and neuropsychiatric SLE (NPSLE) with or without APS all are multisystemic autoimmune disease with similar relapsing–remitting course, affect the same population of patients and may have the same neurological manifestations with multifocal white matter lesions on MRI. Since some patients with APS or NPSLE may be misdiagnosed as MS, this can lead to different treatment modalities. Patients with NPSLE and secondary APS may benefit from combined therapy consisting of immunosuppressive drugs and anticoagulation. Anticoagulation with warfarin is the effective therapy for APS. It is also reported that patients with MS-like disease and aPL had a significant clinical and radiological improvement after anticoagulation. Corticosteroids are used in NPSLE and MS, mostly in active disease. Therefore the clear distinction between three conditions may be difficult influencing the treatment possibilities, which are different, but may affect the disease activity, quality of life and mortality. In the MS differential diagnosis APS and NPSLE should be considered, particularly if atypical clinical features are present. Repeated determination of antiphospholipid antibodies as well as long-term follow-up could be necessary. If persistent positivity of aPL is found or clinical features suggest APS, the 6 months anticoagulation with a target INR of 3–4 is recommended [6,48,52]. See Fig. 2 showing brain MRI of our patients with secondary APS and MS-like disease, evolving into typical MS during several years of follow-up.

2.3. Epileptic seizures

Several studies have demonstrated the association of epileptic seizures and aPL, most of them related to SLE or APS secondary to SLE. Limited data are published concerning epilepsy in patients
with primary APS [31]. Euro-Phospholipid Project Group reported seizures in 7% of 1000 patients with APS [5]. Shoenfeld et al. found epilepsy prevalence in 8.6% out of 538 patients with APS (being 2 times more prevalent in patients with secondary than in primary APS), which is 20 times more than epilepsy prevalence in general population [53]. Most often the occurrence of epilepsy in APS is understood to be the sequella of ischemic neuro-parenchymal insult. It is suggested that underlying ischemic event may be the result of hypercoagulability. Using the neuroimaging techniques the foci of abnormal signals were demonstrated in the white matter of patients with APS [4,31,53]. The immune interaction with the brain tissue is also considered. High titers of aCL, anti-β2GPI and antithrombin antibodies have been reported in epileptic patients. It is reported that purified IgG from APS patients directly permeabilize and depolarize brain synaptoneurosomes [26]. The aPL may interfere with neuronal function binding to neurotransmitters (ATP) as well as by inhibiting the gamma-aminobutyric acid receptor-ion channel complex, which may also increase the neuronal excitability [4,54,55]. Sanna et al. applied the New American College of Rheumatology (ACR) nomenclature for neuropsychiatric SLE [56,57] in 323 patients with SLE and found the prevalence of seizure to be 8.3% in total of 185 patients having neuropsychiatric disease manifestations; aCL were more frequently found in patients with seizures [31]. See Fig. 3 showing brain MRI of one of our patients with SLE and secondary APS presenting with seizures.

2.4. Headache and migraine

Headache is one of the most often described neurologic manifestation in patients with APS, being presented either as a chronic headache or episodes of migraine. The studies investigating the association of migraine and aPL or LA have been controversial. Cuadrado and associates reported the marked improvement of headache in 5 patients with APS and intractable headache after the seven days of anticoagulation therapy [58].

2.5. Chorea

Chorea is reported to be a rare neurologic manifestation in patients with SLE and/or APS, but strongly associated with the presence of aPL [4,31]. Describing their group of 50 patients with APS and chorea, Cervera and associates have found that 58% of patients had SLE, while 12% had a "lupus-like" syndrome. The precipitating factors for chorea were the estrogen containing oral contraceptives (12%), pregnancy (6%) or early postpartal period (2%). In 35% of patients the cerebral infarcts were found on CT and MRI scans [59].

2.6. Cognitive dysfunction in APS

Cognitive dysfunction has been poorly recognized among all other neuropsychiatric manifestations in APS patients. Small series or isolated cases have been mostly described in the context of multi-infarct dementia. Reported are cognitive deficits in SLE patients with limited data on cognitive deficits in APS patients [5]. The most common complaints are poor memory, difficulty in concentrating or keeping the attention for a long time. The recognition of subtle cognitive impairments in APS patients has been facilitated by the neuropsychological assessment mostly in SLE patients [60].

The relationship between cognitive dysfunction and aPL has been investigated. Denburg et al. found that LA positive patients had poor results in verbal memory, cognitive flexibility and psychomotor speed tests and it suggested that this pattern was possibly based on LA related microthrombotic events or vasculopathy [61]. Tekonidou and group showed that cognitive deficits may be found often among the APS patients independent of any other neuropsychiatric manifestation. They also showed that livedo reticularis and...
white matter lesions shown on MRI are associated with great risk for cognitive dysfunction [62]. Menon et al. showed that SLE patients who are persistently positive for aCL with medium or high titer of antibodies had lower scores on a different spectrum of neuropsychologic tests than SLE patients negative for aPL [63].

It is not perfectly clear what is the underlying mechanism of this deficits, recurrent cerebral ischemia or maybe aPL may gain access to the CNS and directly disrupt neuronal function and play a direct role in cognitive impairment like it is shown in experimental studies on animal models [64].

There are some accidental findings of improvement of cognitive function in the APS patients who gain anticoagulation therapy due to other reasons [65] which may support the opinion that arterial ischaemia (thrombosis) represents the primary cause of this neurological manifestations in the aPL positive patients. Although there is no evidence that aggressive anticoagulation should be administered to the APS patients with only cognitive impairment, the anticoagulation treatment with low targeted international normalized ratio (INR) could be beneficial for this group of APS patients. The alternative may be a more benign therapy such as antimarialar or low dose aspirine.

2.7. Catastrophic antiphospholipid syndrome

Catastrophic antiphospholipid syndrome (CAPS)—Asherson’s syndrome is very rare and severe variant of the APS. It is characterized by accelerated small vessel occlusion in the presence of the aPL antibodies usually in high titer [66]. About 1% of patients with APS develop this catastrophic form. CAPS appears in patients with primary APS, SLE, lupus like disease as well as other autoimmune diseases. In almost half of the patients with CAPS it was the first presentation of the APS. Infection, surgery, oral anticoagulation withdrawal, some drugs, obstetric complications, neoplasms and SLE flare are the most common described precipitating factors. Pulmonary, neurological and renal involvement are the most common presenting manifestation of CAPS. Patients usually present with clinical features of severe systemic inflammatory syndrome and rapid development of multiorgan system failure. Acute respiratory distress syndrome, pulmonary embolism and occasional intraalveolar haemorrhage often lead to respiratory failure. Acute renal failure develops as a result of microangiopathy and in some patients renal infarctions. Acute heart failure, valve lesions and myocardial infarction, peripheral arterial and venous thrombosis, gangrene are some of the cardiovascular CAPS manifestations. Livedo reticularis, purpura, and skin ulcers may be present. Liver failure is relatively common. Cerebrovascular accidents, acute encephalopathy and sometimes seizures, headache, silent brain infarcts, venous sinus occlusions are some of the important CNS CAPS features. Differential diagnosis is very complex. The Asherson’s syndrome can mimic or overlap with infection and sepsis, thrombotic thrombocytopenic purpura, severe SLE Flair with CNS involvement and disseminated intravascular coagulation. Because of the progressive and severe course of disease, it is often necessary to initiate treatment before the establishment of the definitive diagnosis. Mortality of CAPS is estimated to be around 44% based on the “CAPS registry data” [67].

3. Treatment of the central nervous system manifestations of APS

Basic approach in the secondary prophylaxis and treatment of primary and secondary APS with CNS involvement is anticoagulation or antiaggregation. In selected cases it is combined with immunosuppression and/or immunomodulation. The treatment should be tailored individually, based on the initial diagnostic workup and follow-up. In difficult cases it is important to form a multidisciplinary team involving rheumatologist, neurologist and haematologist. Accurate diagnosis, exclusion of the infection, identification of the most probable underlying pathogenic mechanisms and possible comorbidities, risk stratification and the assessment of the severity and activity of CNS disease are very important [12,67–70]. In patients with mild or asymptomatic CNS disease, close observation and antiaggregation with low dose aspirin should be considered, particularly in the presence of additional risk factors such as hypertension [71]. Low dose glucocorticoids and hydroxychloroquine or chloroquine may be given to patients with SLE and secondary APS [72]. Statins may be considered, since these drugs may have the potential to prevent some thrombotic incidents in APS by reducing endothelial activation [73]. In patients with severe focal/thrombotic CNS manifestations of APS, a long-term treatment with warfarin is indicated. INR should be kept between 2.5 and 3.0 and only in recurrent thromboembolic incidents over 3.0, though some experts still recommend keeping INR values above 3.0 in all patients with APS and arterial thromboses. In patients with recurrent thrombosis some experts recommend addition of low dose aspirin to warfarine [74]. In difficult cases of thrombotic and nonthrombotic CNS–APS high dose oral or intravenous pulses of glucocorticoids and pulses of cyclophosphamide, plasma exchange and intravenous immunoglobulins should be considered [70]. There are also some reports of successful APS treatment with rituximab [75]. Standard symptomatic therapy should be given to patients as appropriate (anticonvulsants, antidepressants, antidiabetics and anxiolytics, analgesics). It is important to stress the weakness of evidence on how to treat CNS–APS as there are no larger randomized controlled trials [68,76].

References


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