Return to contents page

PRIMARY ANTIPHOSPHOLIPID SYNDROME; DIFFERENTIATION FROM MULTIPLE SCLEROSIS

A Study of 22 Cases

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- **ABSTRACT**

Background/Objective: Anti-phospholipid syndrome (APS) is a well-known cause of thrombosis and can mimic multiple sclerosis (MS). We analyzed the neurologic manifestation, laboratory and MRI findings of our patients with primary APS (PAPS) in an attempt to identify parameters that might differentiate the two entities.
Methods: Of 180 cases with the diagnosis of probable or definite MS,we studied 29 patients who had symptoms suggesting an underlying systemic disease, unusual laboratory findings or atypical evolution for MS.Of these ,22 patients (15 female and 7 male, mean age 30 year) proved to have PAPS with antiphospholipid antibody (aPL) positivity (titer ? 10 GPL units) and were followed-up for at least 8 months. Brain MRI was performed in all of the patients.
Results: The most frequent initial manifestations were paresis (10 cases) and cerebellar signs (4 cases). During the established stage,15 cases had paresis; and cerebellar signs, depression and sensory disturbance were seen in 10, 9 and 8 patients respectively. High ESR,thrombocytopenia and prolonged partial thromboplastin time (PTT) were detected in 8, 4 and 3 patients respectively.MRI of the brain showed multiple lesions in 15 and a single lesion in 7 cases.Also 4 of the female patients had a history of unexplained fetal loss.
Conclusion: We believe that all cases with the initial impression of MS who present with systemic or laboratory features of APS or a history of unexplained fetal loss should be screened for the presence of aPL, and APS should be considered as an alternative diagnosis to MS.

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Key Words • Antiphospholipid syndrome • antibodies, antiphospholipid • multiple sclerosis

Introduction

APS is a thrombophilic disorder in which thrombosis can affect vessels of almost any organ. [1-3] Patients with PAPS have no clinical or laboratory evidence of other definable autoimmune diseases.[4] Neurological involvements rank second in frequency in PAPS and cerebral ischemia is the most common manifestation of the disease.[5-8] Serologic markers are aPLs[9,10] and a positive test is based on IgG (or IgM) phospholipid titer, measured as GPL or MPL units by ELISA.[11 14] Classification criteria for definite APS as proposed by Alarcon-Segovia[15] are: 1) Two or more clinical manifestations including signs of thrombosis, recurrent fetal loss, thrombocytopenia, livedo reticularis and leg ulcer 2) High level of aPL 3) Age of <50 years Although PAPS and MS are usually distinguishable , in some cases distinction between the two diseases based on clinical grounds and brain MRI is not clear; some patients with PAPS may remain unrecognized because the syndrome and its prevalence has not been adequately reported in the primary care literature.[16 21] The goal of this study is to investigate neurologic and systemic manifestations as well as laboratory findings in patients with PAPS that presented as MS or MS-like illness for better differentiation of the two entities.

Materials and Methods

Patients:

Over a 3-year period (1996-99), of 180 cases with the diagnosis of probable or definite MS, we found 29 patients who had symptoms suggesting an underlying systemic disease, unusual laboratory findings for

MS or atypical evolution of MS.

Paraclinical investigation:

Paraclinical assessments included measurement of aPL by ELISA, serologic studies for autoimmune disorders, complete blood count including platelets and ESR. Two-dimensional echocardiography and extracranial carotid arterial doppler studies were done in all 29 cases to detect the presence of possible thrombi. All patients had brain MRI. An IgG titer of 10-15 GPL units was considered weakly positive, 16-80 as moderately positive and ? 81 as highly positive.

Inclusion criteria:

Cases were accepted as having PAPS only if they satisfied the Alarcon-Segovia criteria.

Follow-up:

All documented cases were re-assessed for their initial neurologic findings and were followed-up for at least 8 months to monitor late neurologic manifestations.

Results

Of the 29 cases, seven were excluded because of loss to follow-up (n=5) or having autoimmune disorders (n=2), and 22 patients (15 females and 7 males) proved to have the inclusion criteria of PAPS with an age range of 17-41 years (Median=30 years).

The neurologic findings during the initial and late (estabilished) stages of the disease are shown in Table 1. Documented but unexplained fetal loss was noted in 4 (27%) of our female patients. Table 2 shows their clinical presentation. Systemic manifestations of APS were seen in 13 (59%) of cases, some of whom had a combination of findings which included livedo reticularis and hypertension in 8 (62%), myocardial infarction in 3 (28%), renal disorder and deep vein thrombosis in 1 (8%) of our patients.

Paraclinical findings:

aPL titers were higher than 10 GPL units in all cases. (Range=11-88 with a median titer of 31). Of these, 5 (23%) had a weakly positive, 15 (68%) a moderately positive and 2 (9%) a strongly positive titer. Abnormal ESR (>20 mm/hr.), thrombocytopenia (platelet count <100000) and prolonged partial thromboplastin time (PTT) were seen in 8 (36%), 4 (18%) and 3 (14%) of our cases, respectively. Single and multiple lesions on brain MRI were seen in 7 (32%) and 15 (68%) of cases respectively. The correlation between the number of these lesions with that of neurologic manifestations is shown in Table 3. Two-dimensional echocardiography performed in 14 of our cases disclosed no intra-cardiac thrombi and carotid doppler studies showed no significant stenosis.

Discussion

Thrombosis, the main complication of APS can affect vessels of all sizes and almost all organs.[15] Cerebral ischemia is the most common arterial thrombotic manifestation.[22,23] In fact, an IgG-aPL titer of higher than 10GPL units has been shown to be an independent risk factor for the first stroke by the Antiphospholipid Antibodies in Stroke Study Group(APASS).[11,24] It occurs mainly at a younger age than the typical atherothrombotic cerebrovascular events[6,8,11,25] with women being affected slightly

more than men.[26] The median age of our cases was 30 years with 64% within the age range of29 -37 years The female to male ratio was 2:1. Paresis (mono-, hemi-, parapresis) was the most common presentation during both the acute and established stages. An interesting feature in our cases was the presence of cerebellar signs which is rarely reported in the literature. In this study, they ranked only second to paresis in frequency. Sensory disturbance in the form of numbness and paresthesia was the third most common symptom, localized mainly in the extremities.

Small vessel occlusion of the retinal vasculature results in retinal ischemia and infarction.[27] Certain cases of amaurosis fugax and optic neuritis of vascular origin have been reported in patients with APS.[22,28] Three patients in our group had transient, unilateral blurring of vision with signs of optic neuritis upon ophthalmologic examination of the affected eye.

Neurological examination in four patients who complained of horizontal diplopia, revealed bilateral internuclear ophthalmoplegia (INO) in two and right INO in one. Epilepsy may occur in APS due to non-thromboembolic phenomena.[28] aPLs have been demonstrated to bind directly to cat brain.[29] Sera containing aPL from SLE patients with seizure, has been shown to reduce a GABA receptor mediated chloride in snail neurons.[22,26,30] Four of our patients had epilepsy; grand mal seizure in three and myoclonic jerks in one. Motor dysphasia was present in three patients, and was the sole clinical manifestation in one.

Long-standing and relatively unresponsive tinnitus was observed in two patients; one of whom had a true vertigo.

Progressive cognitive impairment leading to dementia and transient global amnesia may be associated with APS.[5,22,28] Five of our patients complained of memory loss, mainly in relation to recent events.

Depression has also been associated with aPL.[22,26] It was the most common psychological finding in our patients, and was well controlled with medication. Euphoria with inappropriate laughing presented in one patient and was unresponsive to medication. Urinary problem in the form of urgency, dribbling or retention was observed in four patients; two of them with paraparesis. One of our patients was hospitalized because of decreased levels of consciousness, and later developed several other neurologic signs, her IgG titer was the highest (88 units) among our patients. Fetal loss may occur in patients with APS at any time during pregnancy, although it is more common in the second and third trimesters.[31] Some controlled studies found that APLs are more frequent in women with recurrent abortions.[27,32] Unexplained fetal loss occurred in four (27%) of our female patients; three of them with more than one abortion, had systemic manifestations as well. No correlation between the number of miscarriages and the value of IgG–titer was found in our study.

Laboratory abnormalities such as false-positive VDRL, thrombocytopenia, high ESR and prolonged PTT, have been reported in APS[11] and are more commonly seen in patients with aPLs of over 100 GPL units.[22] We found elevated ESR (22-76 mm/hr), thrombocytopenia (platelet count <100000) and prolonged PTT in eight, four and three patients, respectively. Once again, however, there was no clear relationship between the presence of these laboratory abnormalities and the aPL titer.

Brain MRI studies revealed small foci of high signal intensity in subcortical white matter in many patients. These lesions are non-specific and interpreted mostly as "suggestive of vasculopathy" or "plaques of multiple sclerosis" which suggests that some manifestations of APS may be due to an aPL-brain phospholipid interaction and may not be thrombotic in origin. [12,22,33]

The reported median time for recurrent stroke is 7.9 months, although this period is much shorter for those with an aPL-IgG titer of more than 100 GPL units.[22] The frequency of recurrent events increases with the presence of concomitant hypertension and coronary artery disease.[11] All of our cases were followed up for at least 8 months. During this period, 17 cases had recurrent neurological events. Brain MRI showed multiple lesions in 12 patients. The remaining five patients, however, had only a single lesion. Multiple lesions were also present in the brain MRI in 3 out of the 5 remaining cases with no recurrent event. Thus it seems that the presence of multiple lesions are not always followed by recurrent symptoms. In this study, apart from evaluation of neurological manifestations, we conclude that PAPS and MS are difficult to differentiate on the basis of neurologic manifestations and MRI findings alone. A careful medical history and systemic examination, previous history of fetal loss and abnormal laboratory findings might be helpful in the differential diagnosis, and it would be appropriate to rule out PAPS in all patients with MS.

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Return to contents page