

## **EVOKED POTENTIAL STUDIES IN THE ANTIPHOSPHOLIPID SYNDROME: DIFFERENTIAL DIAGNOSIS FROM MULTIPLE SCLEROSIS**

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## Abstract

**Objective:** The CNS manifestations of the antiphospholipid syndrome (APS) can mimic multiple sclerosis (MS) both clinically and radiologically. We performed evoked potential studies in APS patients and compared them to evoked potential studies in MS patients with similar neurological disability.

**Methods:** Thirty APS patients with CNS manifestations, and 33 definite MS patients of similar neurological disability, underwent visual evoked potentials (VEP), somatosensory evoked potentials (SSEP) in upper and lower limbs (UL, LL), and sympathetic skin responses (SSR) in UL and LL.

**Results:** The neurological manifestations in the APS patients included stroke (N=17), transient ischemic attacks (N=10) or severe headache with multiple white matter lesions on brain MRI (N=3). Abnormal SSEP (LL), and SSR (UL; LL) were seen in APS patients (37%, 27% and 30% respectively) but VEP and UL SSEP were rarely abnormal (10% and 6% respectively in APS vs. 58% and 33% in MS,  $p=0.0005$ ,  $p=0.008$ ). Mean VEP latencies were significantly more prolonged in MS patients (116 ms vs 101 ms,  $p<0.001$ ). Only one APS patient had abnormal findings in all three evoked potentials as compared to 7 patients in the MS group ( $p=0.04$ ).

**Conclusion:** An abnormal VEP is uncommon in APS as compared to MS. Coexisting abnormalities in all performed evoked potentials, as well as in UL SSEP were similarly rare in APS. We suggest that in patients in whom CNS clinical findings are the sole clinical manifestation, and brain MRI findings are compatible with the diagnosis of MS or APS, normal evoked potential tests and especially a normal VEP, may add objective information supporting the diagnosis of APS.

## Introduction

The antiphospholipid syndrome (APS) is characterized by arterial and/or venous thrombosis, recurrent fetal loss and the presence of antiphospholipid antibodies (aPL) [1,2]. The diagnosis of APS is currently based on the Sapporo criteria [3]. Clinical manifestations of APS are diverse and virtually any organ may be involved [2]. A wide spectrum of neurological manifestations has been described in association with APS including transient ischemic attacks (TIAs), strokes, chorea, seizures, impaired cognitive function, transverse myelitis, migraine headache, pseudotumor cerebri, cerebral venous thrombosis and mononeuritis multiplex [2, 4-9]. Due to the diversity of neurological manifestations, the differential diagnosis is wide and in the absence of previous vascular thrombosis or a typical obstetric history the diagnosis of neurologic manifestations as due to APS may be difficult. This is further complicated by the fact that aPL are found at a low frequency in the normal population, at a higher frequency in association with autoimmune diseases, especially in systemic lupus erythematosus (SLE), and in 8-32.6% of multiple sclerosis (MS) patients [10,11,12,13]. APS may mimic MS both clinically and radiologically [9]. MRI brain scans in SLE patients, with and without aPL, and in patients with primary APS may demonstrate white matter focal brain lesions which may be difficult to distinguish from those found in MS [9,14].

Similarly to APS, there is no definite diagnostic test for MS. The diagnosis of MS is based on a combination of clinical and laboratory criteria and exclusion of other diseases that could explain the neurologic condition. Cerebrospinal fluid analysis and brain MRI may aid in the diagnosis [15]. The relapsing forms of MS are considered clinically definite when neurologic dysfunction becomes disseminated in space and time. When there is diagnostic uncertainty, MRI studies and evoked potential studies may provide evidence that the lesions are disseminated in space [16]. Visual and/or somatosensory evoked potentials (VEP, SSEP) and assessment of central autonomic pathways by means of sympathetic skin responses (SSR) may provide support that there is dissemination in space even in the absence of clinical dysfunction [15, 16]. Evoked potential tests detect functional dysfunction such as slow conduction in various neural pathways, as in the optic nerves and the spinal cord. The evoked potentials reflect both the amount of demyelination as well as the extent of axonal loss and are remarkably sensitive to clinically silent lesions [17,18].

Neurological symptoms, physical findings, laboratory tests and MRI scans do not easily distinguish CNS manifestations of APS from MS [9]. Evoked potentials have, to the best of our knowledge, never been used before in the evaluation of patients with APS. We report the results of electrophysiological studies performed in APS patients with CNS manifestations and compared them to electrophysiological studies in MS patients with similar neurological disability.

## Patients and Methods

### Patients

Thirty APS patients (primary APS -20, secondary to SLE -10) with CNS manifestations, fulfilling the Sapporo criteria, and 33 definite MS patients of similar neurological disability underwent electrophysiological studies. These studies are performed as part of our routine assessment in all MS patients and APS patients with CNS manifestations.

APS patients were recruited consecutively from the Rheumatology and Neuroimmunology clinics at the Tel-Aviv Sourasky Medical Center. These patients were diagnosed as APS based on evidence of a stroke with a documented neurologic deficit or evidence of a vascular thrombotic event outside the CNS, or a typical obstetric history, and the presence of aPL (anti-cardiolipin IgG, or anticardiolipin IgM, or lupus anticoagulant) at least on two occasions, at least 6 weeks apart. Anticardiolipin antibodies were performed in different laboratories in outpatient clinics utilizing standard commercial Elisa kits. For each patient the tests were repeated in the same initial laboratory. Lupus anticoagulant was performed for all the patients in a single hospital based laboratory utilizing the APTT with a lupus anticoagulant sensitive thromboplastin, or the dRVVT test.

Patients having clinically definite MS according to clinical criteria of 2 exacerbations together with at least 3 typical lesions on the MRI scan, were recruited from the Neuroimmunology clinic at the Tel-Aviv Sourasky Medical Center.

### Methods

Neurological disability: All patients underwent full neurological examinations. The degree of neurological disability was scored according to the Expanded Disability Status Scale (EDSS) in both MS and APS groups [17,19].

### Electrophysiological studies

All patients underwent an extensive neurophysiological study using Nicolet Viking IV equipment (Madison, WI). The evoked potentials performed included: VEP, SSEP and SSR. VEP was elicited by a pattern reversal checkerboard of black and white squares sized 30' and a screen of 11<sup>0</sup>. Two or more sequences of at least 256 trials were averaged for each eye. Responses were recorded from electrode sites Oz, O<sub>1</sub> and O<sub>2</sub>, using Fz as reference. The latency of the P100 peak and amplitude of P100-N145 wave were measured. Responses were considered abnormal if absent, or if the P100 latencies exceeded 115 msec in at least one eye, or if there was an amplitude difference exceeding 50% between the better and worse eye. SSEP was elicited by square wave pulses of 0.1 msec duration, delivered percutaneously over the median nerves at the wrists and over the tibial nerves at the ankles. The stimulus of lowest intensity that caused a small twitch in the corresponding muscles was used. Two or more sequences of at least 512 trials in the arms and 1024 trials in the legs were averaged. Recording sites for arm stimulation were contralateral C3'/C4' and for leg stimulation – Cz', both referenced to FPz. The measured variables were: in the upper limbs the cortical N20 latency to peak and baseline to peak amplitude, in the lower limbs the latency of the cortical P38 wave and its baseline to peak amplitude. Responses were considered abnormal if N20 or P38 were absent, or delayed to more than 21 msec for N20, 46 msec for P38 in at least one limb, or if there was an amplitude difference of more than 50% between the better and worse side.

SSR was recorded synchronously from both palms and soles following a single supramaximal square wave electrical stimulus of the right median nerve at the wrist [16]. Latency to the first peak and peak to peak amplitude were measured for all four limbs. Responses were defined

as abnormal if absent in any one limb, or if having an amplitude less than 50 % of the contralateral side.

**Brain MR Imaging:** MRI studies, which were available for review for 23 APS and 30 MS patients, were performed in several institutions, on different types of machines and were technically variable. All studies included fast spin-echo (FSE) T2 weighted sequences, which were the primary source of information. When available, proton density weighted and FLAIR sequences were used to increase observation confidence. Lesion load was scored based on a scoring system previously described by Cuadrado et al [9]. Foci and areas of high signal intensity (mostly white matter lesions) were graded according to size and number. The severity score for each focus or area was obtained by multiplying the lesion size grade by the lesion number grade. The sum of these scores comprised the total MRI severity score (Table 1).

**Table 1.**

**Brain MRI grading system**

Size of Lesions	Grade
Just seen (<2mm)	1
Small (2.1-5mm)	2
Medium (5.1-10mm)	3
Large (>10mm)	4
Patchy confluent	5
Number of lesions	Grade
1	1
2-5	2
6-10	3
>10	4
Confluent	1-5

Total severity score = lesion size grade X lesion number grade  
Adapted from Cuadrado MJ et al. Medicine 2000 [9].

All MR images were interpreted by a single observer (YS), in a retrospective and blinded fashion. The degree of brain atrophy was assessed on an arbitrary scale of 0-3 (0=no atrophy, 1=mild, 2= moderate, 3=severe).

**Statistical analysis**

Differences between the groups were determined using Fisher's exact test and t-test, as appropriate. Sub-analyses stratifying for neurological disability and for MRI lesion burden were planned before data collection.

## Results

APS patients recruited in this study were  $48.3 \pm 14.5$  years old. They were mainly female (25/30). Neurological disability, as measured by the EDSS, was mild to moderate, ranging from 0 to 5 (mean  $1.4 \pm 1.7$ ). The corresponding data for the MS patients are given in Table 2.

**Table 2.**

### Characteristics of the APS and MS patients

	APS	MS
Age (years)	$48.3 \pm 14.5$	$36.8 \pm 13.2$
F/M	25/5	20/13
Neurological disability (EDSS)	$1.4 \pm 1.7$	$2.0 \pm 1.6$

The CNS manifestations in the APS patients included stroke in 17 patients, TIAs with multiple white matter lesions on brain MRI in 10 patients and severe headache with multiple white matter lesions on brain MRI in 3 patients. These three patients had a history of recurrent pregnancy loss (n=2) or a thrombotic event outside the central nervous system (arterial thrombosis of hand, n=1). Other APS related events in the APS patients included superficial vein thrombosis in one patient, deep vein thrombosis in four, arterial thrombosis in two (in one patient of the femoral artery leading to below knee amputation), central retinal vein occlusion in one patient, and recurrent pregnancy loss in six cases, including intrauterine death in the third trimester in one patient.

We compared the results of the APS patients to those seen in MS. The percentages of abnormal VEP, upper and lower limb SSEP, and upper and lower limb SSR tests in the MS group (58%, 33%, 45%, 27% and 35% respectively) were higher than in the APS group (10%, 6%, 37%, 27% and 30%). This difference was statistically significant for the VEP and upper limb SSEP tests ( $p=0.0005$ ,  $p=0.008$  respectively, Fisher's Exact test) (Table 3).

**Table 3.**

### The percentage of abnormal evoked potentials for APS and MS patients

Evoked potential	APS	MS	<i>p</i> - value
VEP	10%	58%	0.0005
UL SSEP	6%	33%	0.008
LL SSEP	37%	45%	NS
UL SSR	27%	27%	NS
LL SSR	30%	35%	NS

VEP- Visual evoked potential

UL SSEP- Upper limb somatosensory evoked potential

LL SSEP- Lower limb somatosensory evoked potential

UL SSR- Upper limb sympathetic skin response

LL SSR- Lower limb sympathetic skin response

Exclusion of the 3 APS patients whose CNS manifestation was severe headache did not change the significance of the results (data not shown). Mean VEP latencies were significantly prolonged in MS patients, as compared to APS patients (mean  $116 \pm 18$  ms vs  $101 \pm 9$  ms,  $p < 0.001$ ). VEP amplitudes, SSEP latencies and amplitudes, SSR latencies and amplitudes did not show any reliable trend. Only one APS patient had abnormal findings in all three evoked potentials as compared to 7 patients in the MS group ( $p = 0.04$ , Fisher's Exact Test)

Brain MRI scores ranged from 0 to 65 in the APS patients with an average of  $17.5 \pm 14.3$  and in the MS patients from 4 to 65 with an average of  $30.7 \pm 16.6$  ( $p < 0.01$ , t-test). Scores for brain atrophy ranged from 0 to 3 in the APS patients with an average of  $1.1 \pm 1.0$  and in the MS patients from 0 to 2.5 with an average of  $1.0 \pm 0.9$  (not significant). When stratifying for neurological disability, MS patients with more severe neurological disability (EDSS  $\geq 2$ ,  $n = 14$ ) had significantly more abnormal VEP ( $p = 0.001$ ), SSEP ( $p = 0.04$ ), and SSR tests ( $p = 0.04$ ) as compared to APS patients with an EDSS of  $\geq 2$  ( $n = 13$ ). There were no significant differences between the less disabled MS and APS patients. In patients matched for high lesion burden (MRI severity score  $\geq 20$ , MS  $n = 20$ , APS  $n = 7$ ) there were more abnormal VEP ( $p = 0.04$ ), SSEP ( $p = 0.02$ ), and SSR ( $p = 0.02$ ) tests in the MS group. In patients with low lesion burden (MRI severity score  $< 20$ , MS  $n = 10$ , APS  $n = 16$ ) only abnormal VEP tests were significantly more common in the MS patients ( $p = 0.02$ ).

## Discussion

The present study is the first systematic study of evoked potentials in APS patients. The results of this study demonstrate that abnormal VEP and UL SSEP are quite rare in APS patients. Indeed the optic nerves and spinal cord seem not to be commonly affected in APS (as opposed to MS). Coexisting abnormalities in all performed evoked potentials were similarly rare in the APS patients. Ten APS cases had completely normal electrophysiological results and in those with abnormal findings an abnormality was demonstrated in a single test in 13 cases, in two tests in 5 cases and in three tests in only in 1 case.

Our APS patients had similar neurological disability to the MS patients, therefore it was interesting to compare their electrophysiological results. MS and APS are autoimmune conditions which affect similar age groups (age 20-50) and may have similar neurological manifestations [2, 9,15]. There are no definitive diagnostic tests for either condition and the diagnosis relies on a combination of clinical manifestations, laboratory tests, imaging and the exclusion of other conditions. Moreover, brain MRI interpretation by the radiologist as compatible with the diagnosis of MS may mislead the clinician. Additional modalities may not be helpful in the differential diagnosis. Analysis of cerebrospinal fluid for oligoclonal bands is not specific for MS, and similarly the presence of aPL itself, which may be found in 8-33% of MS patients, is neither specific nor diagnostic of APS [13,20]. Two large studies tested MS patients for aPL antibodies and clinical manifestations. They found aPL antibodies in 2% and 15% of the patients respectively and no predominance of any clinical manifestation [21,22]. These results do not support the hypothesis suggested by Karussis et al. that MS patients with aPL antibodies represent a new subgroup of patients [23]. In the latter study atypical clinical manifestations such as persistent headache were more suggestive of a vascular etiology [23]. Since a controversy still exists in the literature regarding the specificity of headache as a manifestation of APS [8, 24] we re-analysed our data excluding the 3 APS patients whose CNS manifestation was severe headache. Exclusion of these patients did not change the significance of the results.

Although the clinical neurologic disability, as demonstrated by EDSS scores was similar in both groups of patients, MS patients had more extensive evoked potential abnormalities. By use of clinical and MRI stratification it was possible to demonstrate that these differences were more pronounced in patients with more severe neurological disability and a higher white matter lesion load on brain MRI. This finding is compatible with more severe and widespread involvement of myelin in MS which is unlike the punctate vascular lesions expected in APS.

The APS patients we recruited were older than the MS patients, leading to a 12 year age difference between the two groups. Although this was not our intent, this age difference, however, may further support the significance of our observations, since one might expect more abnormal electrophysiological tests in the older age group, while we were able to show a smaller percentage of abnormal tests in this group.

In a clinical setting it may often be important to make a dichotomous diagnosis early on since treatment is fundamentally different in the two conditions and assigning incorrect treatment may be dangerous since beta-interferon treatment in SLE and other autoimmune diseases may lead to severe exacerbation of the disease [25]. On the other hand lifelong anticoagulation, commonly used in APS, entails the risk of hemorrhage, while withholding anticoagulation in APS entails a high risk of recurrent thromboses which may be fatal [2,26].

Evoked potentials testing offers simple, inexpensive, objective and quantitative data regarding the distribution of functional systems affected and may detect involvement of systems poorly visualized by neuroimaging. In MS it is now well established that apart from

the lesions clearly seen on T2 weighted images, there is diffuse white matter disease demonstrated by MR spectroscopy or more modern diffusion MR techniques such as high-b value diffusion [27,28]. The use of such techniques in the differentiation of MS from APS is currently under investigation by several groups [29]. Physiologically, the present results indicate that MS is a diffuse white matter disease, while APS seems to affect the brain in a more restricted and focal manner. The differences observed in the present study may indicate qualitative as well as quantitative differences between MS, which affects sensory tracts, while APS may affect cortex and motor tracts. This observation may be relevant to the pathogenesis of the autoimmune damage to the brain in the two disorders. The involvement of a myelin directed reaction seems central in MS, while APS may involve more vascular and neuronal specific mechanisms [30].

We suggest that in patients in whom central nervous system clinical findings are the sole clinical manifestation, and brain MRI findings are compatible with the diagnosis of either MS or APS, normal evoked potential tests and especially a normal VEP, may add objective information supporting the diagnosis of APS. Our results are based on the study of patients with a clear cut clinical diagnosis. It remains to be seen whether electrophysiological studies could help in making the correct diagnosis in more complicated cases or early in the course of the disease.

Competing interest statement: There are no competing interests.

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