

# Central nervous system involvement as the presenting manifestation of autoimmune rheumatic diseases: an observational study using the American College of Rheumatology nomenclature for neuropsychiatric lupus

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## Abstract Objective

We sought to describe CNS involvement as initial presentation of autoimmune rheumatic diseases using a standardized nomenclature.

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## Patients and methods

A 6-year observational study (1999-2005) was conducted in the University Hospital of Heraklion Crete, a regional referral secondary/tertiary care academic center. Patients presenting with new neurological symptoms of acute/sub-acute onset underwent clinical and laboratory screening for systemic autoimmune disorders. The diagnosis of an autoimmune rheumatic disorder was based upon the American College of Rheumatology (ACR) classification criteria, whereas for primary antiphospholipid syndrome (PAPS) we used the Sapporo preliminary criteria. In order to describe the neurological syndromes we used the ACR nomenclature for neuropsychiatric lupus.

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## Results

During this period fourteen patients (ten females and four males) were recorded. Eight patients had systemic lupus erythematosus (SLE), four had primary APS and the remaining two had systemic vasculitis. Four out of the eight SLE patients had secondary APS. Two of them presented with movement disorder (chorea). The other two and all four patients with primary APS presented with cerebrovascular disease (CVD). These six patients comprised the 5.7% of young adults under < 45 years old with cerebrovascular accident admitted over the 6-year period.

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## Conclusions

SLE and APS either primary or secondary to SLE were the most common underlying systemic autoimmune rheumatic diseases, in patients presenting with a neurological event of acute onset. Young adults (< 45 years old) with CVD should undertake screening for SLE/APS.

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## Key words

Neuropsychiatric disease, antiphospholipid syndrome, initial, cerebrovascular disease.

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## Introduction

Neurological symptoms, particularly those that relate to central nervous system (CNS) involvement, are not uncommon during the course of systemic autoimmune rheumatologic diseases. They may precede, coincide or follow their diagnosis (1, 2, 3) which often affect young and middle aged adults. Because patients with these disorders may rapidly deteriorate, the need for urgent and rapid diagnosis and treatment is of paramount importance. However, disease onset may be insidious and the initial symptoms may be vague or atypical requiring a great index of suspicion to assure early diagnosis.

Because of the heterogeneity of autoimmune disorders that can affect the CNS and the variation in their clinical presentation, the use of predefined classification criteria and a widely acceptable nomenclature are essential. Although it is well known that a variety of neurological manifestations can occur during the course of autoimmune rheumatic diseases, few studies have addressed systemically the issue whether CNS involvement can be an initial presentation of these diseases. Knowing the presenting clinical features and their relative frequency in an unselected population that seeks medical care may facilitate early diagnosis and treatment.

In this paper, we describe 14 patients seen in the University Hospital of Heraklion Crete between 1999 and 2005, whose initial symptoms were neurological and who were subsequently diagnosed with a systemic autoimmune disease.

## Patients and methods

We reviewed the charts of all patients admitted to the Neurology Department of our hospital over a six- year period (1999-2005).

**Inclusion criteria:** The main inclusion criterion was patients with a newly appearing neurological event involving CNS of acute/subacute onset. We defined "acute event" as a series of neurological symptom(s) appearing/evolving over 48 hours. Respectively an "event of subacute onset" was

defined as a series of neurological symptoms appearing/evolving over 48 hours-3 weeks. In this respect, patients considered for further evaluation were those with the following diagnoses: Cerebrovascular Disease (CVD), Epilepsy (E), Myelopathy (M), Demyelinating Disease (DD), Headache (H), Cranial Neuropathies (CN) and Various (V). In the last category we included patients presenting with acute confusional state, syncope and dizziness/vertigo.

**Exclusion criteria:** Patients presenting with Peripheral Nervous System involvement of acute/subacute onset (i.e. polyneuropathy, Guillain-Barre syndrome, myopathy, myasthenic syndromes) or exacerbation of a chronic disease (i.e. migraine attacks, seizures in a patient with longstanding epilepsy, multiple sclerosis relapses) were excluded. We also excluded all patients with hereditary or metabolic diseases, patients with a diagnosis of CNS infection (encephalitis, meningitis) and patients with known systemic diseases (i.e. diabetes mellitus) that developed neurological symptoms as a consequence of their primary entity.

Detailed neurological and physical examination was performed in all patients. Symptoms regularly recorded were those listed in the modified version of the Connective Tissue Disease Screening Questionnaire (4). In particular the presence of arthralgias, morning stiffness, joint swelling, Raynaud's phenomenon, oral ulcers, rashes, photosensitivity, pleuritis, hair loss, skin thickening, xerostomia, xerophthalmia were systemically sought. A rheumatologic consultation was always sought when symptoms or physical signs (i.e. hair loss, arthralgias, malar rash) coupled with abnormal laboratory results (see below) raised suspicion of an underlying autoimmune systemic disease.

Initial laboratory studies, performed in every patient admitted to the Neurology Department, included complete blood counts, erythrocyte sedimentation rate (ESR), measurement of prothrombin (PT) and activated partial thromboplastin time (aPTT), routine blood chemistries, liver and renal function tests, electrolytes, total proteins,

cholesterol, LDL, HDL, triglycerides, thyroid function tests, vitamin B<sub>12</sub> and folate levels, HIV titers, Lyme serology and VDRL. Patients with a history of anemia, thrombopenia or leucopenia were specifically screened for an underlying autoimmune disease.

Additional laboratory screening for systemic autoimmune disorders, performed in every patient that met the inclusion criteria, included RF, CRP, ANA, anti-ds DNA, ANCA, C3, C4, IgG/IgM anti-cardiolipin antibodies (aCL), IgG/IgM anti-beta 2 glycoprotein antibodies ( $\beta_2$  GPI), lupus anticoagulant (LA). Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using HEp-2 cells as a substrate. Precipitating antibodies to extractable nuclear antigens (ENA), including Ro/SSA, La/SSB, U1 small nuclear RNP, and Sm, were detected by ELISA, when clinically indicated. LA activity was detected by coagulation assays, adhering to the guidelines of the International Society on Thrombosis and Haemostasis (5). Anticardiolipin (IgG and IgM aCL) and  $\beta_2$ -glycoprotein I antibodies (IgG and IgM  $\beta_2$ -GPI) were detected by a commercially available enzyme-linked immunosorbent assay (ELISA, Aesku lab Diagnostica, Germany), using native human cardiolipin and  $\beta_2$ -glycoprotein I respectively. In addition, a search for other hypercoagulable states (including assessment of fibrinogen, protein C, protein S, activated protein C resistance and antithrombin III) was also carried out. The rheumatologist consultant evaluated abnormal immunological tests.

Lumbar puncture and cerebrospinal fluid (CSF) analysis were performed as indicated. Neuroimaging studies included brain CT and/or MRI scan, extracranial Doppler ultrasonography, transcranial Doppler (TCD), 12-lead ECG, transthoracic and/or transesophageal echocardiography. MR angiography and/or conventional angiography of the neck and cerebral vessels were performed in selected cases.

The diagnosis of specific systemic autoimmune disorders, such as SLE and Wegener granulomatosis, was

established according to American College of Rheumatology (ACR) classification criteria (6, 7, 8). The final diagnosis was based on the expert opinion of two rheumatologists with experience in these diseases (D.T.B., H.K.). The preliminary classification criteria for definite antiphospholipid syndrome of an international consensus workshop held in Saporro, Japan were used for the diagnosis of primary antiphospholipid syndrome (PAPS) (9). Only patients with two positive measurements of LA and aCL within three months were included for further study. For the diagnosis of catastrophic antiphospholipid syndrome (CAPS) the preliminary criteria proposed and accepted in the 2002 International Taormina Consensus Statement on Classification and Treatment of CAPS were followed (10). The diagnosis of other rheumatologic diseases (primary Sjögren's syndrome, systemic sclerosis, rheumatoid arthritis) was made according to established criteria. For the description of the neurological syndromes we used the American College of Rheumatology (ACR) nomenclature for SLE induced CNS syndromes (11).

## Results

### *Demographic and epidemiologic data*

During the six-year period (1999-2005) 4252 patients were admitted to the Neurology department. Of these 2364 fulfilled the inclusion criteria (1800 had cerebrovascular disease, 200 had epilepsy, 124 had a demyelinating disease, 65 had headache, 60 had myelopathy and 115 had various diagnoses). Among those we identified 14 patients (10 females and 4 males) with initial neurological symptoms and subsequent diagnosis of a systemic autoimmune disease. The age of the patients ranged between 16 and 72 years (mean age ( $\pm$  SD)  $39 \pm 16$ ). The median time from the onset of symptoms to the final diagnosis was approximately 5.5 months (range 1 week -12 months).

### *Clinical diagnoses*

As shown in Table I, 8 out of 14 patients fulfilled the ACR criteria for systemic lupus erythematosus (SLE). Four of these also had secondary

antiphospholipid syndrome (APS). Four patients fulfilled the Sapporo preliminary criteria for primary APS. The remaining two patients had systemic vasculitis (Wegener granulomatosis and microscopic polyangiitis). Details of the laboratory findings and neuroimaging studies are shown in Table II.

### *Clinical features*

Of the eight SLE patients, two presented with a cerebrovascular disease (CVD), two with movement disorder (chorea) and each one with seizure disorder, transverse myelitis, headache and demyelinating syndrome. The four patients with CVD (patients 1 and 3) and with hemichorea (patients 4 and 14) had SLE and secondary APS. All four patients with primary APS presented with a cerebrovascular disease. The first patient with systemic vasculitis was a 40-year-old male who presented with tonic-clonic seizures and aseptic meningitis. Five months later, the patient developed right pleural effusion and renal involvement with microscopic hematuria, proteinuria and active urine sediment. Renal biopsy revealed focal-segmental, necrotizing, extracapillary glomerulonephritis that confirmed the diagnosis of Wegener granulomatosis. The second patient with systemic vasculitis, a 72-year-old male, had a 2-year history of "idiopathic pulmonary fibrosis" and c-ANCA positivity. He presented with left hemiparesis due to right striatocapsular infarction (distribution of perforators of right middle cerebral artery). During hospitalization, he had another ischemic infarct in the distribution of perforating branches of left middle cerebral artery. MR angiography and digital subtraction angiography of cerebral arteries were normal. He developed glomerulonephritis with proteinuria, hematuria and red blood cell casts. The diagnosis of microscopic polyangiitis was based on ANCA positivity, pulmonary and renal involvement and the absence of upper respiratory tract involvement and granuloma formation. Although the relative frequency of patients presenting with CVD due to an underlying autoimmune rheumatic disease is relatively low (7/1800, 0.4%),

**Table I.** Clinical features and diagnosis.

AA	Gender, Age	Initial neurological manifestations	ACR nomenclature	Relevant symptoms/signs	Neurological symptom duration prior to diagnosis	Final diagnosis
1	F, 50	R hemiparesis, sensory changes	Cerebrovascular disease	Raynaud phenomenon, headache, hair loss	1 month	SLE+sec APS
2	F, 39	Generalized tonic-clonic seizures	Seizure disorder	Malar rash, photosensitivity, arthralgias spontaneous miscarriages (x2)	12 months	SLE
3	F, 24	L hemiparesis	Cerebrovascular disease	Malar rash, ecchymosis (thrombocytopenia), arthralgias synovitis	1 week	SLE+sec APS
4	F, 17	R hemichorea	Movement disorder	Malar rash, synovitis, photosensitivity, R limb deep vein thrombosis, glomerulonephritis, myocarditis	12 months	SLE+sec APS
5	F, 43	L hemianopia, dysarthria, hemiparesis, hypesthesia	Cerebrovascular disease	Raynaud phenomenon, popliteal artery embolism, ARDS (pleural effusion, intralveolar hemorrhage), ARF, myocardial infarction	15 days	Catastrophic APS
6	F, 39	Coma, tetraplegia	Cerebrovascular disease	Spontaneous miscarriages (x2)	24 days	Primary APS
7	F, 51	Vertigo, gait ataxia	Cerebrovascular disease	Vertigo	20 days	Primary APS
8	M, 59	Diplopia, L facial sensory loss	Demyelinating syndrome	Palpable purpura, synovitis	12 months	SLE
9	M, 42	Generalized tonic-clonic seizures	Seizure disorder	Headache, pleural effusion, glomerulonephritis	1 month	Wegener granulomatosis
10	M, 72	L hemiparesis, dysarthria	Cerebrovascular disease	Pulmonary fibrosis, ARDS, livedo reticularis, hematuria with active urine sediment	2 months	Microscopic polyangiitis
11	F, 16	Paraparesis, vibration and pain sensation loss below T4	Myelopathy	Raynaud phenomenon, malar rash, synovitis, hair loss	3 months	SLE
12	F, 30	Severe tension-type headache	Headache	Fatigue, vitiligo, malar rash, arthralgias, spontaneous miscarriages (x2), synovitis, photosensitivity	8 months	SLE
13	M, 39	Left hemisensory loss, sensory ataxia	Cerebrovascular disease	—	6 weeks	Primary APS
14	F, 27	Right hemichorea	Movement disorder	Oral ulcers, synovitis, perioral choreic movements amaurosis fugax, migraine	12 months	SLE+sec APS

*Abbreviations:* ARDS: Adult Respiratory Distress Syndrome; ARF: Acute Renal Failure.

in adults younger than 45 years old with CVD this frequency is considerably higher (4/70, 5.7%). To put this into a prospective, the relative frequencies for those with epilepsy, myelopathy, demyelinating disease and headache in our cohort were 2/200 (1%), 1/60 (1.66%), 2/124 (0.8%), 1/65 (1.5%) respectively.

#### *Patient management and outcome*

Patients with SLE or systemic vasculitis were treated with steroids alone or

in combination with pulse cyclophosphamide therapy as previously described (12-14). Azathioprine or mycophenolate mofetil were used as maintenance therapy. All patients responded to therapy with no evidence of relapse at follow-up. All patients with primary antiphospholipid syndrome received oral anticoagulation with acenocoumarol (target INR: 2.0-3.0), without experiencing bleeding complications. Two of the patients with SLE and secondary antiphospholipid syndrome

(pt 1 and 3) were given oral anticoagulation in addition to their immunosuppressive therapy, whereas the remaining 2 female patients with hemichorea, apart from immunosuppressive drugs, received antiplatelet agents. (acetylsalicylic acid, ASA).

#### **Discussion**

To our knowledge, this is the first study to use the recently proposed ACR nomenclature for defining the neurological syndromes in neuropsychiatric

**Table II.** Neuroimaging studies and laboratory findings.

AA	CT/MRI	CSF	Platelet count K/MI	IgG/ IgM aCL	IgG/ IgM $\beta_2$ -GPI	LA	ANA	ENA	ANCA
1	L parietal hemorrhage, R parietal (MCA), L occipital (PCA) ischemic infarcts	–	–	26 GPL/ml IgM: –	–	+	1/80	–	–
2	Multiple T <sub>2</sub> lesions (peri-ventricular, subcortical parietal)	ND	N	–	IgG: – 40 U/ml	–	1/320	Sm (+) SSA (+) SSB (+)	–
3	R parietal-temporal (MCA) ischemic infarct	ND	42,000	139 GPL/ml IgM: –	IgG: – 150 U/ml	+	1/160	–	–
4	CT: N, MRI:ND	NA	122,000	–	–	+	1/1280	Anti-DNA (+)	–
5	R and L parietal-temporal (MCA), L parietoccipital (PCA)	ND	90,000*	–	–	+	–	–	–
6	Thalami, brainstem, R occipital (top of the basilar artery) ischemic infarct	ND	N	–	+	+ <sup>§</sup>	–	–	–
7	R cerebellum (PICA) ischemic infarct	ND	N	20 GPL/ml 13 MPL/ml	IgG: – 43 U/ml	+ <sup>§</sup>	–	–	–
8	Multiple T <sub>2</sub> lesions (peri-ventricular, CC, brainstem, C6-C7)	↑ IgG index	N	IgG: – 209 MPL/ml	–	–	1/160	Anti-DNA (+)	–
9	N	↑ WBC (LY), ↑ protein	N	–	–	–	–	–	c-ANCA
10	L and R IC, L parietal-temporal (MCA) ischemic infarcts with SHC	ND	high N	–	–	+	–	–	c-ANCA*
11	High intramedullary signal in T <sub>2</sub> C5-T3	↑ WBC (LY), ↑ protein	N	–	–	–	–	–	–
12	Multiple T <sub>2</sub> lesions (periventricular occipital horn)	N	N	NA	30 U /ml IgM : –	NA	1/40	NA	–
13	L parietal lobe (MCA) ischemic infarct	ND	N	43.6 GPL/ml 6.7 MPL/ml <sup>§</sup>	173.0 U/ml 9.6 U/ml <sup>§</sup>	+ <sup>§</sup>	–	–	–
14	3 T2 lesions (L pulvinar, splenium, L subcortical parietal area)	ND	N	114 GPL/ml 16 MPL/ml <sup>§</sup>	110 U/ml 15 U/ml <sup>§</sup>	+ <sup>§</sup>	–	–	–

\*on admission N.

<sup>§</sup>twice in at least 6-week interval.

N: normal, NA not available; ND: not done; CSF: cerebrospinal fluid; CC: corpus callosum; LY: lymphocytes; C: cervical; aCL: anticardiolipin antibodies; LA: lupus anticoagulant; ANA: antinuclear antibodies; anti-DNA: anti-dsDNA antibodies; ANCA: antineutrophil cytoplasmic antibodies; MCA: middle cerebral artery; PCA: posterior cerebral artery; PICA: posterior inferior cerebellar artery; IC: internal capsule; SHC: secondary hemorrhagic conversion; APL: antiphospholipid antibodies.

*Evaluation:* aCL IgM: Negative < 10 MPL/ml; Weakly positive: 10-25 MPL/ml; Positive: > 25 MPL/ml; aCL IgG: Negative < 10 GPL/ml; Weakly positive: 10-25 GPL/ml; Positive: > 25 GPL/ml;  $\beta_2$  GPI IgM: Negative < 10 U /ml; Weakly positive: 10-25 U /ml, Positive:> 25 U /ml,  $\beta_2$  GPI IgG: Negative < 10 U/ml; Weakly positive:10-25 U /ml, Positive: > 25 U /ml, LA: Negative: LA1-LA2 < 8sec, Positive: LA1-LA2 > 8sec.

SLE (11) for the entire spectrum of the autoimmune rheumatic diseases in patients with CNS involvement at presentation. Our data were collected in a prospective manner and relate to a relatively homogenous population that shares the same environmental and genetic background. In addition, our study cohort, regarding both the sample size and length of follow-up, is representative of the spectrum of patients that seek medical attention due to CNS involvement in a general hospital. The

University Hospital of Crete is a secondary/tertiary regional referral center for the island of Crete covering a population of approximately 600,000. Because of the absence of neurological departments in smaller, secondary care hospitals in the island, patients with significant neurological problems are referred to the University Hospital. Patients with CVD as the initial neurological manifestation comprised the majority in our cohort (7/14, 50%). Four out of 7 were younger than 45

years old and were mostly (3/4) females. All had antiphospholipid syndrome either primary or secondary to SLE, except for the one patient with microscopic polyangiitis. In addition they all had ischemic infarcts with one patient (pt 1 with SLE+ sec APS) also developing a lobar hemorrhage. Five of them had anterior circulation (hemispheric) involvement. The remaining two, both with primary APS, had posterior circulation (brainstem) infarcts. The normal results of Doppler ultra-

sound of neck arteries, MR angiography, ECG and transthoracic ultrasonogram excluded large artery atherosclerosis or cardioembolism as likely causes. In addition there was no evidence of hypercoagulability except for that related to the presence of antiphospholipid antibodies or lupus anticoagulant. The second most common diagnosis in patients with SLE and secondary APS was chorea confirming its specific relationship with antiphospholipid antibodies (15). Both our patients were females in early adult age (17 and 25) with no history of rheumatic fever or oral contraceptive intake. Chorea was unilateral and improved markedly with the combination of acetylsalicylic acid (ASA) and steroids without lack of additional treatment with neuroleptics such as haloperidol.

In a review of the recent literature, we identified a few studies using the ACR nomenclature for neuropsychiatric SLE (NPSLE) to describe the prevalence of the various neuropsychiatric syndromes. In a cohort of 128 SLE patients of Mexican/American ethnicity, Brey *et al.* (16), found 80% to have features of neuropsychiatric SLE. Headache (57%), cognitive dysfunction (79%) and psychiatric disorders were the most common NPSLE syndromes seen, whereas only 2% had cerebrovascular disease, 16% partial seizures and 1% chorea. The mean disease duration at study entry was 8 years. Ainiala *et al.* (17), in a population-based study covering an area with 440,000 people, studied 46 Finnish patients with a definite diagnosis of SLE aged 16 to 65 years and came to similar results. At least one NP syndrome was identified in 42 patients (91%) with the most frequent manifestations to be cognitive dysfunction (81%), headache (54%) and mood disorder (43%). However seizures were found in 9%, cerebrovascular disease in 15%, demyelinating syndrome in 2%, myelopathy in 3% and chorea in 2%. The mean disease duration since diagnosis of SLE was  $14 \pm 8$  years. Afeltra *et al.* (18), studying 61 Italian SLE patients, found 44 patients (72%) with current or past neuropsychiatric manifestations. Fifteen out of the 61 patients (25%) had sec-

ondary APS and in their vast majority (93%) had neuropsychiatric features. The most common neuropsychiatric syndromes were cognitive dysfunction (52%), mood disorder (27%), cerebrovascular disease (27%) and headache (21%). Seizures were found in 11% and myelopathy in 3% of the patients. Mean disease duration was 10 years. In all these studies the prevalence of SLE patients with initial neuropsychiatric disorders is not reported. Thus it is difficult to compare their findings to our results, whereby cerebrovascular disease was the most frequent manifestation. Unfortunately patients in our cohort lacked a standardized neuropsychological evaluation and thus, those with mild cognitive impairment or not overt psychiatric features may have been missed. In addition, we focused on CNS involvement, so we excluded patients with polyneuropathy. However mood disorders, cognitive impairment or polyneuropathy are rarely the initial manifestation of autoimmune diseases. They usually appear later in the course of the disease, as it is confirmed by the above studies.

The diagnosis of antiphospholipid syndrome (APS), either primary or associated with SLE was encountered in 8 out of 14 patients (57.1%). Females presenting with a cerebrovascular disease were the great majority of these patients (5/7). These findings are in accordance with those of Sanna *et al.* (19), who found that cerebrovascular accidents, seizures and headache were independently associated with antiphospholipid antibodies. Similarly, in a European cohort of 1,000 patients with APS (53.1% with PAPS and 36.2% with SAPS) approximately 20% presented with cerebrovascular disease at onset, whereas only 3.6% with epilepsy. Chorea was never the presenting symptom but appeared in 1.3% of the patients, especially with early disease onset (< 15 years old). Catastrophic APS occurred in 0.8 % of the patients (20). Patients with cerebrovascular disease had a positive lupus anticoagulant, rather than anticardiolipin or anti- $\beta_2$ GPI, confirming its reported association as a stronger risk factor for such events (21). We administered oral anti-

coagulation in patients with APS presenting with a cerebrovascular disease of arterial origin targeting an INR between 2.0 and 3.0. This target range was significantly smaller than the target range 2.5-3.5 proposed by Khamashta *et al.* (22), but is in accordance with more recent studies, which favor medium intensity anticoagulation (23). In our experience this treatment was both efficacious in preventing recurrent stroke and safe, since it was not associated with any hemorrhagic complications.

Our study has two main limitations. First we have not established surveillance net and secondly we did not scrutinize the population of interest nor the clinical practice in primary care centers to accurately depict the actual incidence/prevalence of the numerous rheumatic diseases identified via neurological symptoms as the initial presentation. As a result, the number of patients we have studied may be an under-representation of the actual cases. It is possible that older patients with atypical syndromes were not referred to us due to a small index of suspicion. The latter may be also responsible for the lack of other diagnoses (Sjögren syndrome, polyarteritis nodosa) that may also initially - albeit rarely - present with CNS symptoms. In spite of these limitations, we believe that we captured the majority of the cases, since it is common practice in Greece, to refer patients with an acute or subacute onset of neurological symptoms to secondary/tertiary neurology departments.

In conclusion, in an unselected population with neurological symptoms of acute/subacute onset, we showed that young (< 45 years old) patients, especially females, presenting with cerebrovascular disease may harbor SLE and/or APS. Therefore a thorough investigation should be undertaken in order to detect an underlying systemic autoimmune rheumatic disease. In such cases a rheumatologic consultation may facilitate diagnosis and early treatment.

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