

Chorea in Systemic Lupus Erythematosus

José Fidel Baizabal-Carvalho, MD, MSc,* Marlene Alonso-Juarez, MD,† and Michael Koslowski, MD*

Background: Chorea is recognized as one of the neurologic manifestations of systemic lupus erythematosus (SLE). Most reports show an association between chorea and antiphospholipid (aPL) antibodies in SLE patients.

Objectives: The objective of this study was to describe the association of aPL antibodies with lupus chorea and its possible role in the pathogenesis of chorea.

Methods: We made a retrospective review of all cases of lupus chorea between 1989 and 2007 in a tertiary care center in Mexico City.

Results: We found 7 episodes of chorea in 5 patients with SLE. In 2 patients (3 episodes), chorea was associated with cerebral ischemia; one of these cases had positive anticardiolipin (aCL) immunoglobulin G (IgG) antibodies, whereas the other was diagnosed as having vascular lipohyalinosis as the probable cause of cerebral ischemia. In 3 patients (4 episodes), an immune-mediated mechanism was suspected; these cases had negative aPL at the onset of chorea, but IgM aCL antibodies became positive later.

Conclusions: In most episodes, chorea seems to be immunologically mediated and was associated with a later appearance of IgM aCL antibodies. Chorea in patients with lupus may also be caused by cerebral ischemia, and in some cases, it may be associated with IgG aCL antibodies.

Key Words: chorea, basal ganglia, movement disorders, systemic lupus erythematosus, antiphospholipid syndrome, anticardiolipin antibodies, neuropsychiatric lupus

(*J Clin Rheumatol* 2011;17: 69–72)

BACKGROUND

Movement disorders are rare in systemic lupus erythematosus (SLE), yet many kinds of them have been described in the literature, including parkinsonism, dystonia, tics, and tremor¹; however chorea is the most commonly reported, with a frequency between 1% and 4%.²

Chorea in SLE has been traditionally associated with antiphospholipid (aPL) antibodies and/or secondary aPL syndrome (APS). The serologic profile of aPL antibodies in this kind of patient varies; most reports indicate that immunoglobulin G (IgG) anticardiolipin (aCL) is the main antibody related to lupus chorea^{2,3}; other authors have emphasized the importance of lupus anticoagulant in these patients.⁴ The aim of the present study was to describe the association of aPL antibodies with lupus chorea and its possible role in the pathogenesis of this manifestation.

METHODS

A retrospective review of all patients diagnosed with SLE was conducted in a single institution in Mexico City, between 1989 and 2007. We used an international standard codification

to identify all patients with chorea and SLE within the study period. Possible cases before 1989 were excluded, because charts were frequently incomplete and patients were not tested for aPL antibodies. The study protocol was approved by the local ethics committee.

All patients fulfilled the diagnostic criteria of the American College of Rheumatology (ACR) for SLE,⁵ although 2 of them were not identified with 4 or more ACR criteria at the onset of chorea, and thus at that time, they were called as “probable” SLE.

The diagnosis of chorea was conducted on clinical grounds by a team of rheumatologists, psychiatrists, and neurologists with experience in neuropsychiatric SLE and based on the ACR criteria for neuropsychiatric SLE.⁶

The presence of aCL antibodies IgG and IgM was determined in all patients by enzyme-linked immunosorbent assay using cardiolipin as antigen (Sigma Chemicals, St Louis, Missouri) (reference ranges, IgG: 0–20 GPL [IgG phospholipid units]; and IgM 0–10 MPL [IgM phospholipid units]). Lupus anticoagulant was tested only in cases of prolonged activated partial thromboplastin time. The APS was defined according to established clinical and laboratory criteria.⁷

RESULTS

We report 7 episodes of chorea in 5 SLE patients; the mean age at the onset of chorea was 27.8 years (range, 19–38 years). Table 1 resumes the clinical, serologic, imaging, and treatment characteristics of the 7 episodes. Two patients had 2 episodes: cases 1 and 3. None of the patients had a recent history of oral contraceptives consumption. Patient 4 was noted to be pregnant at the onset of chorea.

In cases 2, 3, and 4, chorea was the first manifestation of SLE. In case 1, chorea appeared 3 months after the onset of the mucocutaneous manifestations of lupus. In case 5, chorea appeared 19 years after the SLE onset, complicated with lupus nephritis and difficult-to-control hypertension. Except for case 5, all patients had nonneurologic manifestations of SLE during the chorea (Table 1).

Cases 2 and 4 did not accomplish 4 or more criteria for SLE at the chorea onset; thus, a “probable” lupus disease was diagnosed at that time; however, both cases were confirmed as SLE according to the ACR criteria in the next 2 to 4 months.

In case 1, aPL antibodies were not determined during the first episode; during the second episode, this patient tested negative for aCL IgG and IgM; however, the aCL IgG became mildly positive 6 months after the second episode (16 GPL) and tested positive thereafter.

Cases 2, 3, and 4 tested negative during the episodes of chorea; nonetheless, they tested positive for IgM aCL antibodies 3 to 5 months after the chorea onset and persisted positive thereafter with negative IgG aCL. In case 5, aPL antibodies were negative before, during, and after the chorea episode. Only case 2 tested positive for lupus anticoagulant, and only case 1 accomplished the criteria for secondary APS. No patient had any clinical thrombotic event before the chorea episode.

Four of our 5 cases had another neurologic manifestation during the chorea episode. Case 1 had a transient ischemic attack during the first episode, manifested with aphasia, and right-side

From the *Department of Neurology, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; and †Department of Surgery, National Institute of Medical Sciences and Nutrition, “Salvador Zubirán,” Mexico City, Mexico.

No funding was received for this study.

Correspondence: José Fidel Baizabal-Carvalho, MD, MSc, 47-83 Boulevard de l'Hôpital, Paris Cedex 75651 France. E-mail: baicarjf@gmail.com.

Copyright © 2011 by Lippincott Williams & Wilkins

ISSN: 1076-1608/11/1702-0069

DOI: 10.1097/RHU.0b013e31820e7c8d

TABLE 1. Clinical, Serologic, and Imaging Findings in the 7 Episodes of Chorea

Case	Sex and AAO, yr	No. Episodes	Duration (Distribution) of Chorea	(Episode) Other CNS Manifestations During the Chorea	Other Nonneurologic SLE Manifestations During the Chorea	APS and aPL Antibodies	CNS Imaging Findings	(Episode) Treatment
1	F/19	2	4 wk (Bilateral)	(1) TIA	Malar rash, photosensitivity	aCL IgG became positive 6 mo after the 2nd episode, APS	Territorial infarcts without involvement of basal ganglia (MRI)	(1) Prednisone 60 mg/d CF in monthly pulses; aspirin 180 mg/d (2) Haloperidol 10 mg/d
2	F/25	1	12 wk (Unilateral, left side) 5 wk (Bilateral)	(2) Silent stroke Psychosis, seizures	Proliferative nephritis Positive ANA Lymphopenia (700/ μ L)	aCL IgM became positive 3 mo after the episode of chorea IgG negative	Normal (MRI)	Dexamethasone 15 mg/d
3	F/38	2	2 yr (Bilateral)	Aseptic meningitis (1) Psychiatric disturbance	Oral ulcers	aCL IgM became positive after the 2nd episode IgG negative	Normal in both episodes (CT/MRI)	Valproic acid 1000 mg/d Ziprasidone 40 mg/d (1) Haloperidol 10 mg/d
4	F/19	1	3 mo (Unilateral, right side) 1 yr (Bilateral)	(2) Cerebellar syndrome and high CSF proteins Status epilepticus	Hair loss Lymphopenia (1200/ μ L) Proliferative nephritis Lower-limb vasculitis Arthritis	aCL IgM became positive 5 mo after the episode IgG negative	Normal (CT)	(2) Haloperidol 10 mg/d Prednisone 25 mg/d CF in monthly pulses; aspirin 150 mg/d Prednisone 60 mg/d
5	F/38	1	6 mo (Unilateral, right side)	Stroke	Positive ANA and dsDNA antibodies None	Negative aPL antibodies	Lacunar infarct on the left lenticular nucleus (MRI)	Valproic acid 1200 mg/d Haloperidol 15 mg/d

AAO, age at onset of chorea; ANA, antinuclear antibodies; APS, antiphospholipid syndrome; CF, cyclophosphamide; CT, computed tomography; dsDNA, double-stranded DNA; F, female; M, male; TIA, transient ischemic attack.

hemiparesis that recovered within 12 hours; a magnetic resonance imaging (MRI) scan at that time did not show abnormalities. Three months later, during the second episode of chorea, she had a silent ischemic stroke affecting the territory of the right posterior cerebral artery, demonstrated with MRI. Five months after the onset of the second chorea episode, the patient had a right parietal stroke manifested by left-side hemiparesis and hemisensory deficit; an echocardiogram and carotid ultrasound ruled out intracavitary thrombus and carotid plaques, respectively.

In case 2, psychosis accompanied the first episode of chorea; the patient also had generalized tonic-clonic seizures lasting 2 minutes; a lumbar puncture carried out 3 days after the onset of these manifestations revealed mild pleocytosis (leukocytes: 25/ μ L), with normal glucose, proteins, and opening pressure; the cerebrospinal fluid (CSF) cultures were negative.

In case 3, the patient had clear psychiatric manifestations with aggressiveness, emotional lability, easy crying, and echolalia; these symptoms lasted 4 months and had a slow resolution. During the second episode of chorea, the patient showed a cerebellar syndrome with incoordination, dysarthria, and dysmetria, along with the reappearance of some psychiatric manifestations including echolalia. A lumbar puncture revealed an increased protein content in the CSF (73 mg/dL), with normal glucose, opening pressure, and no leukocytes.

In case 4, the patient had a generalized tonic-clonic status epilepticus that lasted approximately 10 hours; 3 days later, bilateral chorea was observed. In case 5, chorea was the only neurologic manifestation; however, a stroke on the left basal ganglia was suspected with a computed tomography scan and confirmed through MRI (Fig. 1).

Despite the relatively long duration of chorea in some patients, cases 1, 3 (both episodes), and 5 showed a significant improvement within 10 days with low doses of dopamine antagonists, and none developed tardive dyskinesias. Case 2 was treated with valproic acid and had a complete resolution of the chorea within 5 weeks. In case 4, haloperidol was not given because of possible risks to the fetus; this case had a slow resolution

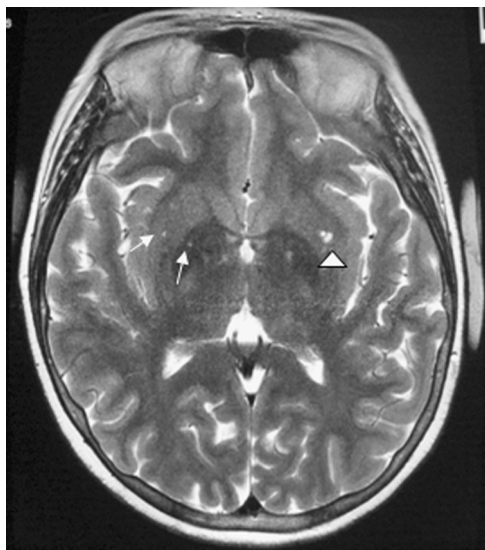


FIGURE 1. Case 5. A 38-year-old woman with a long history of SLE. T2-weighted MRI shows a lacunar infarct (arrowhead) on the left lenticular nucleus; a temporal-associated right hemichorea was seen in this case. Small lesions on the right basal ganglia of possible ischemic origin are observed (arrows).

of the chorea in 12 months. Cases 1 (episode 1), 2, 3 (episode 2), and 4 were also treated with moderate to high doses of corticosteroids, mainly because of systemic lupus activity. Cases 1 and 3 were treated with monthly pulses of cyclophosphamide because of comorbid proliferative nephritis. Cases 2 and 4 were also treated with valproic acid because of generalized epileptic seizures. A significant improvement in the nonneurologic manifestations was reported in all cases within the next 4 weeks.

DISCUSSION

An evidence of the role played by aPL antibodies in lupus chorea is mainly related to a temporal association on clinical grounds.² Studies in animal models have shown that aPL can depolarize synaptoneuroosomes⁸; furthermore, contralateral striatal hypermetabolism has been demonstrated in a patient with primary APS and alternating hemichorea⁹; these studies support the concept of a direct activation of the basal ganglia circuits mediated by aPL. In cases 2, 3, and 4, we suspect an immune-mediated disorder. Nevertheless, it is difficult to assume a causative role of aPL antibodies in these patients as they tested negative at the time of chorea presentation. The IgM antibodies can reach the central nervous system (CNS) only if a previous disruption of the blood-brain barrier (BBB) exists. These antibodies can simply represent an epiphenomenon and/or an immunologic response to tissue destruction. Cases of chorea with positive aCL IgM and negative IgG have been described, although not commonly.³

Another potential pathogenic mechanism for lupus chorea is ischemia affecting the basal ganglia or the tracts connecting the basal ganglia, thalamus, and cerebral cortex. Some of these ischemic events might be related to thrombosis mediated by IgG aCL antibodies²; this is the mechanism for chorea that we propose for case 1. In case 5, right hemichorea was associated with a small infarct in the left lenticular nucleus (Fig. 1). Lipohyalinosis in lenticulostriate arteries, secondary to chronic hypertension, was assumed to be the cause. Cerebral ischemia as the pathogenic mechanism of chorea is considered infrequent in SLE patients.¹⁰

In our study, other neuropsychiatric manifestations such as seizures, stroke, and psychosis were noted. These symptoms could be related to the multiple effects of pathogenic antibodies in the CNS involving cortical and subcortical structures. It seems plausible that these patients had a vulnerable BBB, leading to passage of antibodies to the CNS. It is notable that some of the neurologic manifestations accompanying chorea and observed in our patients may disrupt the BBB, including seizures, aseptic meningitis, and stroke.

Case 3 also showed signs of cerebellar involvement. A pathologic study carried out in a patient with chorea and APS showed a remarkable decrease in Purkinje cells and neurons of the basal ganglia.¹¹ Interestingly, a relationship between chorea and cerebellar syndrome might exist in patients with SLE, as both conditions have been associated to direct damage by aPL, antineuronal, and/or Purkinje-cell antibodies.^{11,12}

Psychiatric disturbance as in cases 2 and 3 could be partially explained by immunologic damage into the limbic and associative circuits that interconnect the frontal cortex with the basal ganglia.¹³

CONCLUSIONS

Chorea in patients with lupus may result from an immunologic-mediated mechanism or ischemia. In the first case, disruption of the BBB may have an important role, facilitating the entrance of antibodies to the CNS. The aPL antibodies, although frequently reported in these cases, have not yet proved a direct

pathogenic role and other antibodies reacting with the glutamate receptor *N*-methyl-D-aspartate as the anti-double-stranded DNA antibodies¹⁴ could be implicated in the neurologic manifestations. Ischemia as the mechanism of chorea in lupus seems to be less frequent.¹⁰ It could be mediated by IgG aPL antibodies and strategic infarcts disrupting the cortical–basal ganglia–thalamus–cortical circuit, or it could be the result of vascular damage secondary to a long-term SLE evolution with associated vascular risk factors.

REFERENCES

- Martino D, Chew NK, Mir P, et al. Atypical movement disorders in antiphospholipid syndrome. *Mov Disord.* 2006;21:944–949.
- Cervera R, Asherson RA, Font J, et al. Chorea in the antiphospholipid syndrome: clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. *Medicine (Baltimore).* 1997;76:203–212.
- Orzechowski NM, Wolanskyj AP, Ahlskog JE, et al. Antiphospholipid antibody-associated chorea. *J Rheumatol.* 2008;35:2165–2170.
- de la Fuente-Fernández R. Lupus anticoagulant and chorea. *Neurology.* 1997;49:639–640.
- Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25:1271–1277.
- ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum.* 1999;42:599–608.
- Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum.* 1999;42:1309–1311.
- Chapman J, Cohen-Armon M, Shoenfeld Y, et al. Antiphospholipid antibodies permeabilize and depolarize brain synaptosomes. *Lupus.* 1999;8:127–133.
- Furie R, Ishikawa T, Dhawan V, et al. Alternating hemichorea in primary antiphospholipid syndrome: evidence for contralateral striatal hypermetabolism. *Neurology.* 1994;44:2197–2199.
- Galanaud D, Dormont D, Marsault C, et al. Brain MRI in patients with past lupus-associated chorea. *Stroke.* 2000;31:3079–3083.
- Kuroe K, Kurahashi K, Nakano I, et al. A neuropathological study of a case of lupus erythematosus with chorea. *J Neurol Sci.* 1994;123:59–63.
- Shimomura T, Kuno N, Takenaka T, et al. Purkinje cell antibody in lupus ataxia. *Lancet.* 1993;342:375–376.
- Joel D. Open interconnected model of basal ganglia–thalamocortical circuitry and its relevance to the clinical syndrome of Huntington's disease. *Mov Disord.* 2001;16:407–423.
- DeGiorgio LA, Konstantinov KN, Lee SC, et al. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. *Nat Med.* 2001;7:1189–1193.