

# Antiphospholipid Antibody-Associated Chorea

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**ABSTRACT.** *Objective.* To describe the clinical features, treatment, and outcomes of patients with antiphospholipid antibody (aPL)-associated chorea.

*Methods.* The study cohort consisted of consecutive patients with chorea evaluated between 1990 and 2005 with documented aPL at time of their neurologic diagnosis.

*Results.* Eighteen patients were identified, 4 with systemic lupus erythematosus (SLE). The 14 non-SLE patients experienced 1.6 vascular thromboses/pregnancy losses per person, while patients with SLE experienced 0.5 events/person. Four non-SLE patients (29%) and no SLE patients met criteria for antiphospholipid antibody syndrome (APS). None of these 4 tested positive for IgM anticardiolipin antibody (aCL). In contrast, 10 (71%) non-APS patients tested positive for IgM aCL. Chorea was most often bilateral, mild to moderate, and occurred once with a median age at onset of 44 and 33 years in non-SLE and SLE patients, respectively. Therapy included immunosuppression in 3 (21%) non-SLE patients and in all SLE patients. Antidopaminergic agents were used in 7 (39%). All patients responded to treatment. Five patients received anticoagulation for thrombosis and 2 died of bleeding complications, both non-SLE patients.

*Conclusion.* aPL-associated chorea occurs most often in women and severity is mild to moderate. Clinical expression of chorea does not differ between those with and without SLE. Anticoagulation should be reserved for thrombosis treatment and not simply for chorea in the presence of aPL, as 2 patients died of bleeding. The absence of IgM aCL in patients with APS supports prior evidence that IgG aCL and lupus anticoagulant may be the more clinically relevant antibodies for thrombosis. However, IgM aCL may be important in patients with chorea. (First Release Oct 15 2008; J Rheumatol 2008;35:2165–70; doi:10.3899/jrheum.080268)

## Key Indexing Terms:

ANTICARDIOLIPIN ANTIBODY      CHOREA      ANTIPHOSPHOLIPID ANTIBODIES  
ANTIPHOSPHOLIPID ANTIBODY SYNDROME      LUPUS ANTICOAGULANT

Chorea is a hyperkinetic movement disorder characterized by rapidly flowing, chaotic movements of one or more portions of the body. Chorea is a well known but rare manifestation of systemic lupus erythematosus (SLE), and is thought to occur in less than 2% of such patients<sup>1,2</sup>. This phenomenon was first reported in 1941 in a 16-year-old girl<sup>3</sup>. The association between chorea and the presence of lupus anticoagulant (LAC) was first described in 1983 in the original description of antiphospholipid syndrome (APS)<sup>4</sup>. A study from the European Phospholipid Project Group examining a cohort of 1000 patients with APS, including both primary and secondary forms, demonstrated that chorea is indeed rare, developing in only 13 of these patients<sup>5</sup>.

Individual case reports and case series illustrating this association have described highly variable clinical characteristics and outcomes<sup>5-8</sup>. We report our experience in patients with antiphospholipid antibody (aPL)-associated chorea.

## MATERIALS AND METHODS

*Study cohort.* Patients seen at Mayo Clinic, Rochester, Minnesota, between January 1, 1990, and December 31, 2005, with a diagnosis of chorea who tested positive for aPL or had a prior diagnosis of APS were screened for inclusion in the study. Patients were identified through a central diagnostic index using the following search terms: antiphospholipid antibody, lupus anticoagulant, anticardiolipin antibody, and antiphospholipid syndrome. The same diagnostic index was queried for the term chorea. These 2 lists were then cross-referenced, yielding our potential patient cohort. The complete electronic and paper medical records of each patient were abstracted by the primary author. Data collected included patient demographics and relevant clinical, laboratory, and imaging information at diagnosis of chorea through last followup.

All patients authorized the use of their medical records for research purposes, and the study was approved by the Institutional Review Board.

*aPL testing.* Anticardiolipin antibody (aCL) titers of IgM or IgG were considered positive if  $\geq 1:8$  for those tested prior to 2001<sup>9</sup>. Since 2001, IgM and IgG concentrations have been reported as MPL (IgM phospholipid units) and GPL (IgG phospholipid units) with a positive value considered to be  $\geq 40$ , indicating medium to high titer<sup>10</sup>. The presence of a LAC was defined by published criteria<sup>9</sup>. Anti- $\beta_2$ -glycoprotein I (anti- $\beta_2$ -GPI) antibody testing was not performed, as it was not widely recognized as part of

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the aPL screen at the time of evaluation. All measurements of aPL were recorded, including the results of repeat testing when available.

**Description of chorea.** Presence of chorea was determined by a neurologist. The description included whether movements were unilateral or bilateral, involved the upper or lower extremities or both, and whether there was head or face involvement. Symmetry was recorded if movements were bilateral. We wanted to characterize the degree of severity of choreiform movements, but since there was no validated clinical score for this purpose, we devised the following scale based on our experience: mild: no impairment in activities of daily living or interruption of work; moderate: some impairment in activities of daily living or interruption of work; severe: unable to perform activities of daily living and/or requiring hospitalization for chorea. The number of episodes was recorded as 1 or more than 1. Duration was defined as the total time from symptom-onset to date of resolution or last followup. Response was defined as no response (NR) if choreiform movements remained the same; partial response (PR) if movements diminished while receiving treatment; or complete response (CR) if movements disappeared. Major bleeding was defined as an episode requiring hospitalization and/or resulting in death.

## RESULTS

In total 2314 patients were identified with aPL and/or APS and 405 patients were identified with chorea. Cross-referencing these 2 lists yielded 21 patients. After full chart abstraction, we excluded patients with Sydenham's chorea ( $n = 2$ ) and one patient with a neurodegenerative syndrome and no chorea, resulting in a total of 18 patients. Four of the 18 patients had SLE, and the remainder will be referred to as non-SLE patients.

Ten non-SLE patients (71%) were female, with median

age at onset of chorea of 44 years. Median followup time was 9 months. Table 1 gives the patients' thrombosis history and immunologic characteristics. The 14 non-SLE patients experienced a total of 4 venous thromboses, 6 arterial thromboses, and 12 pregnancy losses, for an average of 1.6 events per person. All thromboembolic events occurred prior to the onset of chorea, with the exception of 2 strokes, which are indicated in Table 1. Antinuclear antibody (ANA) testing was positive in 4 patients; double-stranded DNA (dsDNA) was positive in 2 patients and not performed in 4; extractable nuclear antigen (ENA) tests were either negative or not performed. These patients were taking various medications at the time chorea began as listed in Table 1. None of these 14 patients had signs or symptoms of SLE and none went on to develop SLE within the followup period.

In comparison, 50% of SLE patients were female, with a median age at onset of chorea of 33 years. They experienced 2 strokes prior to onset of chorea for a total of 0.5 events per person, but no other thromboembolic events. All had positive ANA and dsDNA tests. Three of the 4 tested positive for LAC and aCL and one tested positive for LAC only. Three of the 4 were taking prednisone 10 mg per day or less when chorea began.

Of the 14 non-SLE patients, 4 (29%) had persistently positive aPL and fulfilled all criteria for definite APS<sup>10</sup>. In contrast, none of the SLE patients met criteria for definite APS. Of the 4 patients with APS, none tested positive for

Table 1. History of thrombosis and immunologic characteristics at time of evaluation of chorea. All thromboses occurred prior to onset of chorea unless otherwise indicated.

Patient	Sex	VTE	ATE	Pregnancy Morbidity	aPL	Repeat aPL	ANA	dsDNA	ENA	Medications
Non-SLE patients										
1*	M	DVT	CVA	—	LAC	LAC	—	—	—	Isosorbide dinitrate, warfarin, aspirin
2	F	—	—	+1	IgG/M	ND	—	ND	—	Cyclobenzaprine, simvastatin, amitriptyline, meloxicam
3	F	—	—	—	IgM	ND	—	—	—	None
4	F	—	CVA	—	IgG/M/LAC	ND	+	—	—	OCP
5	M	—	—	—	IgG	ND	—	+	ND	None
6	F	DVT	—	+2	IgM	IgM	—	ND	ND	Zolpidem, hydrocodone, gabapentin, trazadone, venlafaxine, bupropion, levothyroxine
7	M	DVT	—	—	IgM	ND	+	—	—	None
8*	F	—	NITEC, CVA <sup>†</sup>	+5	IgG	IgG	+	—	—	Propranolol
9*	F	—	—	+1	LAC	LAC	—	ND	ND	None
10*	M	—	CVA <sup>†</sup>	—	IgG	IgG	—	—	—	Atenolol, fosinopril, sertraline
11	F	DVT	—	+3	IgM	ND	—	—	—	Valsartan
12	F	—	—	—	LAC	Neg	—	—	—	None
13	F	—	NITEC	—	IgG/M	Neg	—	ND	—	None
14	F	—	—	—	IgG/M	ND	+	+	—	HRT
15	F	—	CVA	—	IgG/LAC	ND	+	+	—	Prednisone, phoslo, phenobarbital, omeprazole, warfarin
16	M	—	—	—	IgG/M/LAC	IgM/LAC	+	+	—	Prednisone, zolpidem, ranitidine
17	F	—	—	—	LAC	ND	+	+	+	None
18	M	—	CVA	—	IgG/M/LAC	IgM	+	+	ND	Prednisone

<sup>†</sup> CVA occurred after the onset of chorea. \* Patient with antiphospholipid antibody syndrome. aCL: anticardiolipin antibody; ANA: antinuclear antibody; aPL: antiphospholipid antibody; ATE: arterial thromboembolism; CVA: cerebrovascular accident; DVT: deep venous thrombosis; dsDNA: double-stranded DNA antibody; ENA: extractable nuclear antigen; HRT: hormone replacement therapy; LAC: lupus anticoagulant; NITEC: noninfectious thrombotic endocarditis; ND: not done; OCP: oral contraceptive pill; VTE: venous thromboembolism.

IgM aCL. In contrast, 10 (71%) of the non-APS group had a positive IgM aCL either alone or in combination with another aPL.

*Clinical features of chorea.* Table 2 illustrates the clinical characteristics, treatment, and response to therapy. In all patients, the presentation of chorea was described as subacute, with progressive onset within days to weeks. There were no episodes of abrupt onset. Twelve non-SLE patients (86%) and all SLE patients had mild to moderate disease.

Multiple other neurologic symptoms were present. Patient 1 developed dementia in his eighth decade. Patient 2 had mild generalized ataxia, without other signs of a cerebellar syndrome. Patient 3 had a history of epilepsy as a child. Patients 4, 5, 8, and 9 experienced mild dysarthria. Patient 5 had 2 generalized tonic-clonic seizures, which occurred one year after the onset of chorea. Patients 7 and 14 had a change in personality and became disinhibited. Patient 9 had nonspecific memory loss. Patient 10 had a subcortical mild dementia and memory loss that seemed to coincide with the onset of chorea. Patient 12 had migraine headaches. Patients 11 and 13 had mild dystonia in addition to chorea. Patient 15 had a history of lupus cerebritis.

Patients 16 and 17 had word-finding difficulty. Patient 18 had dysarthria and emotional outbursts.

All patients had magnetic resonance imaging (MRI) of the brain performed at the time of first evaluation at our institution for chorea (data not shown). All but one patient had normal brain MRI or small-vessel ischemic changes of aging that were considered nonspecific and appropriate given the ages of the patients. Patient 4 had increased T2 signal in the high anterior right basal ganglia; she also had unilateral chorea, but it was on her right side.

*Treatment and outcomes of chorea.* Eleven non-SLE patients (79%) received anticoagulation or antiplatelet therapy. Five received warfarin or heparin specifically for a thrombosis that occurred near the time of onset of chorea and not for the treatment of chorea. Aspirin was used for nonspecific reasons at the discretion of the treating clinician in the remaining 6 patients. Immunosuppression was used in 3 non-SLE patients (21%). Antidopaminergic drugs were prescribed to 6 patients (43%) for symptomatic relief of chorea. Assessment of patient outcomes in the non-SLE group revealed a partial response in 8 (57%) and a complete response in the remaining 6 (43%).

Table 2. Clinical features, treatment, and outcomes of antiphospholipid antibody-associated chorea.

Patient	Severity	Location	Symmetry	Head Involvement	Extremities	Episodes, n	Duration, mo	AC/AP	Treatment ISP	Other	Response
Non-SLE patients											
1	Mild	Unilateral	NA	Yes	Upper/lower	1	1	Warfarin	—	Thioridazine	CR
2	Mild	Bilateral	Symmetric	Yes	Upper/lower	1	36	Warfarin	—	—	CR
3	Mild	Bilateral	Symmetric	Yes	Upper/lower	1	24	Aspirin	—	—	PR
4	Mild	Unilateral	NA	No	Upper/lower	1	6	Aspirin	—	—	PR
5	Mild	Bilateral	Asymmetric	No	Upper	> 1	2	Aspirin	—	—	CR
6	Mild	Unilateral	NA	Yes	Upper/lower	> 1	27	—	—	D/C gabapentin bupropion and venlafaxine	CR
7	Mild	Bilateral	Symmetric	Yes	Upper/lower	> 1	12	Aspirin	—	Clonazepam	PR
8	Moderate	Bilateral	Asymmetric	Yes	Upper/lower	1	2.5	Warfarin	Prednisone	—	CR
9	Moderate	Bilateral	Unknown	Yes	Upper/lower	> 1	84	Warfarin	—	—	CR
10	Moderate	Bilateral	Asymmetric	Yes	Upper	1	24	Warfarin	—	Tetrabenazine	PR
11	Moderate	Bilateral	Asymmetric	Yes	Upper/lower	1	7	Heparin	—	Fluphenazine quetiapine	PR
12	Moderate	Unilateral	NA	Yes	Upper/lower	> 1	12	—	Prednisone, azathioprine	Risperidone	PR
13	Severe	Unilateral	NA	No	Upper	1	6	Warfarin	Prednisone	Trihexyphenidyl, carbidopa/levodopa	PR
14	Severe	Bilateral	Asymmetric	Yes	Upper/lower	1	3	—	—	Risperidone	PR
SLE patients											
15	Mild	Bilateral	Symmetric	No	Upper	1	1	Warfarin	Prednisone	Clonazepam	PR
16	Mild	Bilateral	Asymmetric	Yes	Upper/lower	1	4	Heparin	Prednisone, cyclophosphamide	Carbidopa/ levodopa	CR
17	Moderate	Unilateral	NA	No	Upper/lower	1	2	Warfarin	Prednisone, azathioprine, hydroxychloroquine	Clonazepam	CR
18	Moderate	Bilateral	Asymmetric	Yes	Upper/lower	> 1	3	Aspirin	Prednisone	Clonazepam, depakote	CR

AC: anticoagulation; AP: antiplatelet; aPL: antiphospholipid antibody; APS: antiphospholipid antibody syndrome; CR: complete response; D/C: discontinue; ISP: immunosuppression; NA: not applicable; PR: partial response.

Three SLE patients (75%) were taking prednisone at the time of onset of chorea. Treatment in those 3 included increasing the prednisone dose. Additional immunosuppression was used in 2 patients (50%). In combination with the dopamine antagonists listed in Table 2, complete response was achieved in 75%.

There were 3 known deaths, including 2 from major bleeding. All were in the non-SLE group. Patient 10 died of a subdural hematoma while taking warfarin. Patient 11 died of a retroperitoneal hematoma after receiving intravenous heparin for a deep venous thrombosis. Patient 14 died of a myelodysplastic syndrome 3 months after the onset of chorea.

## DISCUSSION

Antiphospholipid antibody-associated chorea is rare. Our series is the largest from a single institution and includes 18 cases collected over 15 years. The Mayo Clinic is a large referral center, which saw over 2300 patients with aPL during the study period. Chorea itself is a rare symptom, with one population-based study reporting a prevalence of < 1% for those aged 50–89 years<sup>11</sup>. Over 400 such patients were seen at our institution during the study period.

Cervera, *et al* reported their experience of aPL-associated chorea along with a review of all reported cases and found that 96% were female, with a mean age of 23 years<sup>12</sup>. The percentage of women in our entire series was lower (67%) and they were older at time of chorea onset, 44 and 33 years in the non-SLE and SLE groups, respectively. This may be the result of excluding pediatric cases. Cervera's group reported ANA and ENA positivity in 82% and 24%, respectively<sup>12</sup>. This is higher than in our series, in which 44% had positive ANA and 6% had positive ENA. This may be because 70% of the patients in that series had lupus or lupus-like disease. In contrast, only 22% of our patients had SLE. In addition, the effect of missing ANA or ENA data in our series may also explain some of these differences.

None of the patients with definite APS in our study were found to have a positive IgM aCL, whereas 71% of the non-APS patients did. The strength and clinical significance of the absence of IgM aCL in the APS patients is difficult to determine with such small numbers, but the association is consistent with other reports that IgG aCL and LAC are more likely to be associated with clinical events in APS than IgM aCL<sup>13-15</sup>. It is noteworthy, however, that chorea did occur in 4 patients who had only an IgM aCL.

A recent study of a large pediatric lupus cohort examined the prevalence of aCL,  $\beta_2$ -GPI, and LAC to determine the clinical association of aPL and neuropsychiatric manifestations of SLE<sup>16</sup>. Of 137 patients, 2 developed chorea and each had a persistently positive LAC. Interestingly, all 4 of our SLE patients had a positive LAC on initial testing. Unfortunately, 2 were never retested at our institution and one was persistently positive. It may be that this association

exists in adults as well, but further prospective studies would be needed for confirmation.

Chorea in both the non-SLE and SLE groups was predominantly mild to moderate. Twelve patients (67%) had only one episode, consistent with other cases in the literature<sup>2</sup>. This perhaps reflects the tendency of aPL levels to wax and wane. A higher percentage of our patients had bilateral involvement compared to the series by Cervera, *et al* (67% vs 55%), which may be explained by the greater severity of cases seen at this institution on a referral basis<sup>12</sup>.

All patients, regardless of treatment, had improvement or resolution of chorea, consistent with previous cases<sup>12</sup>. Based on our series, there does not appear to be a role for anticoagulation in the treatment of chorea in the absence of a thromboembolic event. In our patient cohort, anticoagulation was specifically administered for the treatment of thrombosis and not chorea. Indeed, anticoagulation should be used cautiously, as 2 patients died of bleeding complications. Alternatively, prednisone appears to be effective, but the presence of mild to moderate chorea in the absence of APS does not justify the use of potentially harmful immunosuppressive agents. Symptomatic relief of chorea can likely be achieved with dopamine antagonists, which were effective in all 7 patients in whom they were administered. However, the potential for an irreversible tardive disorder with chronic use of these drugs must be balanced against their benefits.

The mechanism of chorea in relation to the presence of aPL remains unknown. Historically, 2 separate mechanisms of action have been proposed: an ischemic process causing reduced circulation to the basal ganglia; and an immune-mediated neuronal attack as a result of binding of aPL to phospholipid-rich regions of the basal ganglia<sup>17,18</sup>. The evidence against reduced circulation as a cause includes the subacute onset and recurring pattern of chorea, the absence of relevant ischemic changes on MRI, and no clear reason why an ischemic process should uniquely select the circulation of the basal ganglia. In addition, studies using imaging techniques have made the ischemic stroke theory less likely<sup>19-22</sup>. Instead, alterations in striatal metabolism have been observed on positron emission tomography imaging during episodes of chorea<sup>19,20,22</sup>. Indeed, in our own cohort, only one patient had increased T2 signal in the basal ganglia. However, this was present on the ipsilateral side of the choreiform movements and cannot explain the presence of chorea. A more plausible explanation in these cases is that chorea is immune-mediated. Chapman, *et al*<sup>18</sup> demonstrated that purified IgG from patients with high levels of aPL and neurologic symptoms will depolarize neuronal tissue from rat brainstem, evidence that aPL can interact with neuronal tissue directly.

The association between aPL and chorea may be thought to be coincidental. However, chorea without an obvious explanation is extremely rare<sup>23</sup>. In addition, 12 of our

patients (67%) had a spontaneous thrombotic event, suggesting that the antibodies were clinically active and not just laboratory artifact or coincidence. Other traditional risk factors for the development of chorea include medications such as oral contraceptives<sup>24</sup>, or recent infection, such as Sydenham's chorea<sup>25</sup>. One of our patients was taking an oral contraceptive at the time of chorea onset, but it did not resolve upon stopping the medication. Another was taking hormone replacement therapy, but did not stop it when chorea developed. No patient in this series had evidence of an infectious disease at the time of presentation, and hence no test for infectious disease was performed.

With such a rare disease, case-control studies should be performed to determine possible associations or causality. Ideally, we would have compared our 18 patients with chorea and aPL to the 2300 patients at our institution that tested positive for aPL who did not have chorea to determine any potential risk factors or identify any differences in clinical expression of aPL. A previous study from our institution correlated prevalence of aPL with either systemic disease or thrombosis in 664 consecutive patients referred for suspected thrombophilia or unexplained prolonged clotting time, of which 137 tested positive for LAC or aCL or both<sup>9</sup>. The study had a lower number of women (61%) and subjects were slightly older (median age 52 yrs), but there was a similar number of patients with SLE (19%), and they had a similar number of thromboembolic events (69%), compared to our present study. Further, both series demonstrated that SLE patients were more likely to test positive for LAC and aCL (75% and 71%, respectively) than either alone, but this did not translate into a higher number of thromboembolic events. The most notable difference between studies was that no patient was diagnosed with or developed chorea in the previous study<sup>9</sup>. Further, aPL testing revealed LAC-positive alone in 9.5%, aCL-positive alone in 55.5%, and 35% of patients having both antibodies positive, compared to our series, where 4 had LAC alone (22%), 10 had only aCL (56%), and 4 had both (22%). Based on this comparison study, it appears that age, sex, LAC positivity, or having both LAC and aCL may influence a patient's risk of developing chorea. However, adequate sample size and power to assess predictors of chorea development in a multiple logistic regression model would be needed.

Our study has several limitations; it was a retrospective study, and data from the medical records were incomplete and subject to recording bias. In addition, the author who extracted the data (NMO) was aware of the study hypothesis, which could have introduced bias. The scoring system for severity of chorea was not validated, but rather was devised as a simple way to communicate severity in this descriptive study, and would require additional examination. Although our results are derived from a tertiary care institution that often sees complex and rare presentations, and hence are prone to referral bias, the rarity of this disorder

essentially nullifies this as a potential limitation of our study as it would not be possible to observe sufficient numbers in a population-based study. Unfortunately, we were unable to obtain longterm followup and repeat antibody testing for half of these patients since they were all referred to our institution, and subsequently were lost to followup.

The majority of patients with aPL-associated chorea in our study were women who experienced one episode of mild or moderate chorea. The clinical expression of chorea was similar among those with and without SLE. IgM aCL was absent in all patients with APS, consistent with prior evidence that IgG aCL and LAC are more likely associated with thromboses. Anticoagulation should not be used for the treatment of chorea simply in the presence of aPL, and should be reserved for patients who experience a clinical thromboembolic event. Immunosuppression with prednisone and symptomatic relief of chorea with dopamine antagonists appear to be effective. The search for aPL should be considered in patients presenting with chorea given the unique clinical features and potential therapeutic implications.

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