Lupus Anticoagulant, Antiphospholipid Antibodies and Migraine

M.J. Hogan, D.G. Brunet, P.M. Ford and D. Lillicrap

ABSTRACT: The records of fifteen patients referred for neurological assessment and found to have lupus anticoagulant or elevated anticardiolipin antibodies were reviewed. The mean age for females in the group was 29.4 years and for males was 35. A diagnosis of migraine, either as an acute or chronic problem, was made in 10 (66%) of these patients. Seven of the 15 patients had ischemic stroke and two patients had other thrombotic complications associated with lupus anticoagulant. Three of the nine female patients with migraine had histories of spontaneous abortions. All migraine patients experienced transient or more prolonged neurological deficits with their headaches. An association between lupus anticoagulant and migraine can only be suggested. Data on the incidence of migraine in patients with lupus anticoagulant in the general medical population does not exist. Furthermore the prevalence of lupus anticoagulant in migraine sufferers is unknown. Therefore further studies are required to investigate this possible association.

RÉSUMÉ: Anticoagulant lupique, anticorps antiphospholipide et migraine Les dossiers de quinze patients référés pour évaluation neurologique, chez qui on avait mis en évidence un anticoagulant lupique ou un taux élevé d'anticorps anticardiolipine, ont été revisés. Dans ce groupe de patients, l'âge moyen des femmes était de 29.4 ans et celui des hommes de 35 ans. Un diagnostic de migraine a été posé chez 10 (66%) de ces patients, tant chez ceux dont le problème était aigu que chez ceux chez qui il était chronique. Sept des quinze patients avaient fait un accident cérébro-vasculaire d'origine ischémique et deux patients présentaient d'autres complications thrombotiques associées à l'anticoagulant lupique. Trois des neuf patientes migraineuses avaient une histoire de fausses couches. Tous les patients migraineux avaient présenté des déficits neurologiques transitoires ou prolongés accompagnant leurs céphalées. Une association entre l'anticoagulant lupique et la migraine ne peut qu'être suggérée. Il n'existe pas de données sur l'incidence de la migraine chez les patients qui ont un anticoagulant lupique dans la population générale venant à l'attention médicale. De plus, la prévalence de l'anticoagulant lupique chez les patients souffrant de migraines est inconnue. Par conséquent, il est nécessaire de procéder à des études supplémentaires pour investiguer la possibilité qu'une telle association existe.

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Lupus anticoagulant (LAC) is an IgG or less frequently an IgM antibody that belongs to a group of antibodies directed against phospholipid. LAC was first identified in 1952 in two patients with systemic lupus erythematosus (SLE) who were reported to have a bleeding tendency.[1] Espinoza and Hartmann[2] in a recent review reported a prevalence of LAC of approximately 10% in SLE but a wide range (6% to 71%) has been reported elsewhere.[3] LAC has also been identified in patients who do not have other features of SLE. Schleider et al [4] and Gastineau et al [5] reported on 58 and 219 identified cases of LAC respectively and both groups found that approximately half of the patients studied did not have SLE.

Although the LAC has an in vitro anticoagulant effect (by neutralizing the procoagulant phospholipids in the assay system[3]) most patients with these antibodies have a tendency to develop thrombotic complications.[1,3,6] Bleeding is an unusual complication and when it occurs there is usually some other defect in the clotting mechanism.[1,3,5,7] The incidence of thrombosis in SLE patients with LAC has been reported to range from 23% to 58%.[7,8,9] The incidence of thrombosis in SLE patients without LAC is approximately 15%.[9,10] Patients with LAC who do not have SLE have a similar risk for thrombotic complications as patients with both LAC and SLE.[5]

The reason for the thrombotic tendency in patients with LAC has not been determined. There is a strong, but not absolute correlation, between LAC and elevated antibodies to the phospholipid cardiolipin.[11] Elevated anticardiolipin antibody (ACA) levels have been shown to be associated with thrombotic complications.[11,12] Among the theories proposed for the thrombotic pathogenesis of LAC and antiphospholipid antibodies is the inhibition of PGI_2 production by interaction of the antibodies with phospholipid within endothelial cell membranes.[13] PGI_2 is a vasodilator and an inhibitor of platelet aggregation produced by endothelial cells. It has also been suggested that platelets may be predisposed to aggregation secondary to membrane bound antiphospholipid antibody.[20]

From the Departments of Medicine, (Drs. Hogan, Brunet, Ford, Lillicrap) and Pathology (Drs. Ford and Lillicrap) Queen's University, Kingston

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Reprint requests to: Dr. D.G. Brunet, c/o EEG Department, Kingston General Hospital, Kingston, Ontario, Canada K7L 2V7

Central nervous system complications are recognized in LAC patients. These are principally due to cerebrovascular thrombotic events which have been reported to occur in 3% to 18% of patients with LAC.[5,7,14] There are several reports of LAC in young patients presenting with cerebrovascular ischemia with or without other conditions predisposing to stroke.[15,16,17,18,19] Levine and Welch[20] have recently presented a review of 32 reported cases of lupus anticoagulant associated with cerebrovascular ischemia. Twenty-five patients did not have SLE but 15 of these patients were reported to have other definite stroke risk factors.

Migraine associated with LAC was first reported by Brandt and Lessell[21] in 2 of 11 patients with SLE and migraine.

Recently Levine et al[22] reported two cases of migraine with lupus anticoagulant. These patients did not have SLE at the time of assessment. In a review of the literature these authors identified six other cases of migraine occurring in patients with lupus anticoagulant in addition to the cases noted above. They suggest that alteration of platelet membrane phospholipids due to LAC or possibly interaction of LAC with neuronal phospholipid may be responsible for migraine in these patients.

We have recently recognized a group of young patients who presented with histories of migraine and/or neurological deficits (transient or prolonged) who were found to have either LAC or ACA or both. In only a few of these patients were other major risk factors for stroke identified and only one patient has gone on to develop features consistent with SLE. It is the purpose of this paper to present our initial experience with LAC and to suggest a possible association with migraine.

Methods

We reviewed the records of 15 patients seen by the neurology service at Kingston General Hospital who were found to have lupus anticoagulant and/or anticardiolipin antibodies. Twelve of these patients presented since July 1986. In the other three patients LAC had been recognized several years earlier.

The LAC was detected by two methods. Initial screening was done with an activated partial thromboplastin time test (APTT reagent - Actin FS, American Dade). Presence of the LAC was confirmed using Exner's Kaolin clotting time method.[23]

Cardiolipin antibodies were measured by a modification of the ELISA method described by Koike et al.[24] Results were expressed in arbitrary units (AU) where one AU is 1 standard deviation above the mean for the normal control population (50 normal subjects). Values for the IgM and IgG ACA in excess of 3 AU were regarded as positive.

Migraine is a clinical diagnosis and the features of this disorder have been well documented.[25,26,27,28] In this study patients were diagnosed as having classical migraine, common migraine, complicated migraine or basilar artery migraine. Classical migraine referred to a typical migrainous headache following a brief transient neurological deficit while common migraine was not associated with a neurological deficit. In complicated migraine the neurological deficit persisted during and after the headache. The features of basilar artery migraine have been described by Bickerstaff.[28]

Neurological symptoms and signs were considered to be transient if resolution occurred within 24 hours.

Results

The clinical and laboratory data of all 15 patients are summarized in Tables 1 and 2. Twelve of the patients (80%) were female. The average age at the time of diagnosis of LAC was 29.4 years (19 to 49) for females and 35 years for males. A history of migraine was identified in 10 of the 15 patients in this study.

Six patients were initially referred to the neurology service for assessment of headache and migraine was diagnosed in five (cases 1,6,8,9,10). Two of these patients (cases 8,9), who had histories of recurrent thrombotic complications and spontaneous abortions, had already been identified as having LAC but their migraine problem had not been assessed. The remaining patient (case 15) had non-migrainous headache.

Three patients (cases 2,3,4,) developed neurological deficits acutely and a diagnosis of complicated migraine was made after initial investigations failed to identify other possible etiologies for their symptoms and signs. One of these patients (case 3) was recognized to have a long history of common migraine and reported increased severity of headaches in the 6 months prior to her presentation.

One patient (case 5) presented with an acute cerebral ischemic event and was found to have had recent onset of classical migraine. Two other patients (cases 11,13) presented with acute focal neurological deficits and CT head scan evidence of infarcts but did not have a migraine history. Two patients (cases 12,14) presented with fluctuating sensory symptoms and no history of migraine. The final patient (case 7) presented with a four week history of gradually developing hemichoreoathetosis and a 15 month history of migraine. Within the following month she developed sufficient features to establish a diagnosis of SLE.

Seven patients were identified as having ischemic stroke. Four of these cases (1,2,3,5) were from the migraine group. Major risk factors for stroke (apart from antiphospholipid antibodies) were identified in two patients; one was hypertensive (case 13), and the other had diffuse narrowing of the left internal carotid artery on angiography (case 5). No other vascular abnormalities were detected in the stroke group of patients.

The birth control pill (BCP) was used by seven patients, six of them being in the migraine group. Two of the patients with stroke were using the BCP (cases 2,5).

Three female patients (cases 1,6,8) had one or more spontaneous abortions which are a recognized complication of LAC.[3] Two patients (cases 8,9) had experienced considerable morbidity secondary to the thrombotic tendency caused by LAC.

LAC was identified in 12 patients. The three patients negative for LAC (cases 10,11,14) showed evidence of elevated ACA levels. Elevated ACA levels were present in a total of 11 patients. Other serology included the VDRL which was positive in only one case (15). Positive ANA titres were seen in a total of five patients. Three of the migraine group had positive ANA titres including the one patient that has developed SLE (case 7).

Discussion

A total of 10 LAC cases with migraine have been reported in the literature.[22] In our group of 15 patients with LAC migraine was diagnosed in 10. In 7 of these patients migraine was either an acute presenting problem (cases 2,4), had developed over the

Table 1: Clinical Features and Treatment in 15 Patients with LAC or ACA and Neurologic Symptoms

Case No.	Age at Presentation	Sex	Presenting Symptoms and Signs	Headache History	Headache Designation	Arterial or Venous Thromboses	Spontaneous Abortions	BCP Use	Fatigue	Treatment and Course
1.	24	F	Right arm paresis, dysarthria, vertigo, and unsteady gait resolving over three weeks	Throbbing headache preceded by scintillating scotoma and recurring for 8 weeks. Also occurred 5 years earlier	classical migraine	no	yes X1	yes	yes	Propranolol ineffective ASA helped - neurologically stable and fatigue eased Prednisone started in anticipation of pregnancy with reduction of ACA levels
2.	25	F	Right visual field scotoma, expressive dysphasia and right hemiparesis, resolving over several hours, followed by throbbing headache	Recurrence of presenting problem Mild headache monthly since starting BCP one year earlier	classical and complc. migraine	no	no	yes	yes	Diltiazem, propranolol ineffective. ASA helped for two months. LTAC controlled recurrence of neurological deficits but headaches continue
3.	31	F	Generalized headaches followed by right arm hemiparesis, blurred vision, drowsiness and speech problems all resolving in several hours	Recurrent throbbing headaches with nausea, photophobia since age 14	common and complc. migraine	no	no	no	no	ASA ineffective LTAC prevented recurrence of neurological deficits
4.	47	F	Generalized throbbing headache preceded by blurred vision, dizziness, left side paresthesia and loss of consciousness	No other headache history	complc. migraine	no	no	no	yes	Stable on ASA
5.	25	F	Transient loss of consciousness, right hemiparesis, aphasia, resolving over several days	Throbbing headache occasionally preceded by scintillating scotoma, recurring for four months	classical migraine	no	no	yes	no	Neurological deficit recurred and partially resolved over several months
6.	21	F	Frequent (several/day) recurrent headaches with dizziness and diplopia	Same as presenting problem Headaches improved after BCP use stopped	basilar artery migraine	no	yes X1	yes	no	ASA - stable
7.	21	F	Left arm paresis Left hemichoreoathetosis	Recurrent headaches preceded by scotoma for 15 months	classical migraine	no	no	yes	yes	Trihexyphenidyl ineffective Choreoathetosis improved when steroids started for presumed CNS involvement with SLE
8.	25	F	Recurrent transient visual loss, memory loss with mild headaches	Recurrent right sided headaches preceded by scintillating scotoma for 10 years	classical migraine	DVT X3	yes X4	no	occ.	Propranolol controlled headaches Carbamazepine controlled partial comples seizures LTAC following recurrent DVT's
9.	38	M	Peripheral vascular insufficiency	Headaches preceded by scintillating scotoma for 10 years	classical migraine	DVT x2 arterial occlusion X1	n/a	n/a	no	LTAC for DVT's Plasmapheresis, prednisone and cyclophosphamide have been tried to control ACA levels Right below knee amputation due to vascular insufficiency
10.	34	F	Transient dizziness and unsteadiness followed by headache	Recurrent headaches preceded by scintillating scotoma (since childhood) or right arm numbness (for 2 years)	Classical migraine	no	no	yes	no	Cafergot occasionally helps Trial of amitriptyline underway
11.	35	M	Loss of balance, dysarthria, left hemiparesis, transient vertigo and diplopia	No headache history	none	no	n/a	n/a	no	ASA with partial improvement
12.	19	F	Transient left arm numbness	No headache history	none	no	no	yes	no	BCP stopped, no recurrence
13.	35	M	Dysphasia resolving over one week	No headache history	none	no	n/a	n/a	no	ASA - Stable
14.	32	F	Fluctuating symptoms of bilateral visual impairment, small right inferior field defect and "altered sensation" in right arm	Ill defined pressure sensation	none	no	no	no	no	No treatment at this time
15.	49	F	Recurrent right sided head pain since removal of a right sphenopalatine connective tissue mass one year earlier	No other headache history	none	no	no	no	no	Prednisone started and headache eased and CT evidence of reduction in size of remaining connective tissue mass

Abbreviations: ASA — acetylsalicylic acid; ACA — anticardiolipin antibodies; BCP — birth control pill; CNS — central nervous system; complc. migraine — complicated migraine; CT — computerized tomography; DVT — deep venous thrombosis; LTAC — long term anticoagulation with coumadin; SLE — systemic lupus erythematosus

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Table 2. Laboratory Findings in Study Patients

Case No.	Coagulation Parameters PT sec.	PTT sec.	Platelets per litre $X10^{-9}$	Lupus Anticoagulant	Anticardiolipin Antibody (AU) IgG	IgM	Serology ANA	VDRL	Other Investigations
1.	14/12	29	165	positive	>15	5.8	neg.	neg.	CT head — small cerebellar infarcts NCVE — no significant abnormalities Echocardiogram — normal CSF analysis — normal EEG — posterior slow wave excess
2.	12/12	30	380	positive	< 3	< 3	neg.	neg.	CT head — normal Cerebral angiography — normal Echocardiogram — normal EEG — left hemisphere slowing with hyperventilation
3.	13/12	31	247	weak positive	3.2	< 3	neg.	neg.	CT head — left internal capsule hypodensity compatible with infarct EEG — left temporal slow and sharp wave abnormality Echocardiogram — normal NCVE — high velocity at proximal left MCA
4.	12/12	28	299	positive	< 3	< 3	neg.	neg.	CT head — normal EEG — normal CSF analysis — normal Echocardiogram — normal NCVE — moderate turbulence at right common carotid bifurcation
5.	12/12	25	323	weak poositive	< 3	< 3	neg.	neg.	CT head — infarcts in left frontal and left fronto-parietal areas Cerebral angiography — diffuse narrowing of left internal carotid artery EEG — left hemisphere slowing with bursts of delta waves Echocardiogram — normal
6.	13/12	31	151	positive	8	< 3	neg.	neg.	No other neurological investigations
7.	13/13	32	158	positive	11.4	< 3	pos.	neg.	CT head — normal EEG — normal CSF analysis — normal
8.	13/12	29	236	positive	9.2	4.9	pos.	neg.	CT head — widening of right Sylvian fissure EEG — slow and sharp wave focus in right hemishpere
9.	15/11 (LTAC)	39	230	positive	8.8	9.6	pos.	neg.	CT head — calcification in the occipital horn of the left lateral ventricle and a small calcification in the occipital cortex at the same level
10.	12/12	30	280	negative	< 3	4.9	neg.	neg.	No other neurological investigations
11.	12/12	29	359	negative	3.85	< 3	neg.	neg.	CT head — left basal ganglia hypodensity consistent with infarct, also possible subarachnoid cyst over upper portion of vermis of cerebellum NCVE — essentially normal, one study suggested possible turbulence in left IC Echocardiogram — normal Evoked potential studies — normal
12.	12/12	33	158	positive	< 3	< 3	neg.	neg.	NCVE — normal
13.	12/12	52	120	positive	10.8	<3	pos.	neg.	CT head — old right frontal infarct EEG — mild slowing NCVE — normal Echocardiogram — normal
14.	12/12	31	278	negative	< 3	7.8	neg.	neg.	CT head — normal Evoked potential studies — normal NCVE — normal
15.	14/12	28	111	positive	>15	4.5	pos.	pos.	CT head — old infarcts in left frontal and parietal lobes and right centrum semiovale EEG — left fronto-temporal slow and sharp waves Cerebral angiograms (7 years earlier) — normal Echocardiogram (7 years earlier) — normal

Abbreviations:
ANA — antinuclear antibody
CSF — cerebrospinal fluid
CT — computerized tomography
EEG — electroencephalogram
LTAC — long term anticoagulation with coumadin
NCVE — non-invasive cerebrovascular examination (Doppler flow studies)
neg. — negative
pos. — positive
PT — prothrombin time
PTT — partial thromboplastin time
VDRL — venereal diseases research laboratory test

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preceding 15 months (cases 5,6,7) or was a long standing problem that had become more severe in the preceding year (cases 1,3). In the remaining three patients (cases 8,9,10) there was a long unchanging history of migraine. None of the patients in the migraine group suffered from common migraine alone. All of the migraine sufferers had experienced either transient or more prolonged neurological symptoms and signs.

It is possible that several of our cases (2,3,4) who were diagnosed as complicated migraine may have simply suffered from TIA or stroke with an accompanying headache. However the gradual progression of neurological deficits observed in case 2 is much more typical of classical migraine than stroke. Case 3 had clearly suffered from worsening headaches typical of common migraine prior to her presentation. Only case 4 had no previous headache history.

Our group of migraine patients represents a selected population. Four of the 10 patients had suffered an ischemic stroke at a relatively young age. Vascular abnormalities were only identified in one of these patients (case 5). Three of our nine female migraine patients had one or more spontaneous abortions. Two patients had previously suffered deep venous thromboses and one patient developed SLE. However, it must be noted that apart from a tendency for thrombotic complications eight of our ten migraine patients with LAC were otherwise well. It is of interest to also note that three of our patients without other underlying disease reported feeling generally fatigued and that this eased considerably when therapy with ASA was instituted.

The birth control pill was used by 7 of our 12 female patients but without a control population we are unable to comment on any possible significance of this finding.

There was not an absolute correlation between LAC and elevated ACA levels in our patients. This has been recently reported[29] and suggests that we may be looking at a range of antibodies with overlapping activity rather than a single antibody against a specific epitope. In our three ACA positive - LAC negative patients no thrombotic complications or stroke were documented. Otherwise no differences between our LAC negative and LAC positive patients was recognized.

Only two patients had prolonged partial thromboplastin times (PTT). Twelve patients however were positive for LAC using the kaolin clotting time (KCT). This can be explained by the relative insensitivity of the PTT reagent used (Dade Actin FS) to the effects of LAC. Therefore if LAC is suspected clinically a more sensitive test such as the KCT should be performed.

At this time the prevalence of migraine in the population of patients with antiphospholipid antibodies is not known. We also do not know the prevalence of these antibodies in the normal population or the population that attends neurology clinics. Therefore, even in our cases where there had been a recent change in migraine status, we do not know if the association with lupus anticoagulant was merely coincidental or if migraine patients with LAC represent some subgroup of the migraine population with a specific, as yet unknown, pathophysiology. However this data raises the question of a possible association between LAC and migraine and further investigation into this problem is warranted.

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