SHORT REPORT

No evidence of misdiagnosis in patients with multiple sclerosis and repeated positive anticardiolipin antibody testing based on magnetic resonance imaging and long term follow-up

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Objective: To determine whether patients with definite multiple sclerosis (MS) and repeated positive anticardiolipin antibody (aCL Ab) testing fulfil the recently updated criteria for the antiphospholipid syndrome (APS). Also, to determine if these patients form a separate subgroup in terms of long term follow-up and MRI characteristics.

Design: A blinded case control study comparing MRI patterns between aCL Ab positive and negative MS patients with a clinical follow-up of 7 years.

Participants: 8 (5.6%; male:female ratio 2:6; 6 relapsing–remitting subtype, 1 primary progressive subtype and 1 neuromyelitis optica (NMO)) of 143 consecutive patients with definite MS or NMO (71% relapsing–remitting, 18% secondary progressive and 6% primary progressive disease course; 4% NMO) showed repeated positive aCL Ab testing.

Setting: Outpatient clinic of a tertiary MS centre in the Netherlands.

Results: All eight aCL Ab positive patients had levels below 40 MPL/GPL units, with the majority of intervals between tests of at least 12 weeks. After follow-up, none of the patients fulfilled the criteria for APS. No specific MRI features were present compared with 24 matched aCL Ab negative patients.

Conclusions: No aCL Ab positive MS patient fulfilled the criteria for APS, arguing against a possible misdiagnosis or coexistence.

The relevance of anticardiolipin antibodies (aCL Ab) in patients with multiple sclerosis (MS) is still unknown. aCL Ab are antiphospholipid antibodies that initially were linked to thrombosis in systemic lupus erythematosus and first reported by Hughes in 1983.[1 2] Recognised as a separate entity, this condition was labelled ''antiphospholipid syndrome'' (APS). It classically presents as recurrent arterial and venous thromboses and pregnancy losses.[3]

APS and MS may be difficult to distinguish, both clinically and radiologically.[4] An article in the UK based *Times* newspaper reported the results of a survey of the London Lupus Centre suggesting that at least 5% of MS patients were misdiagnosed and suffer from APS instead of MS.[5]

The aCL Ab in MS may herald a misdiagnosis of MS or the coexistence of APS, implying different therapy (anticoagulants) and prognosis. Results may be difficult to interpret because of possible ''mislabelling'' of APS patients for MS patients, and different cut-off values of aCL Ab levels being applied. Moreover, most studies have not examined wide fluctuations of positive aCL Ab samples.[6] To fulfil the criteria of APS, aCL Ab have to be present on two or more occasions at least 6 weeks apart.[7] Recently, the classification criteria for APS have been revised; to further minimise transient and irrelevant Ab levels, the interval between the tests should now be at least 12 weeks.[3] Surprisingly, only two of 10 studies in MS patients have reported repeated testing of aCL Ab.[8 9] No study has reported repeated testing after at least 12 weeks.

The aim of our study was to determine whether the presence of aCL Ab in patients with definite MS is associated with specific long term clinical and radiological features and whether the criteria for APS are met. In patients with definite MS and positive aCL Ab on repeated testing, we evaluated clinical features and longer term evolution of MS. In addition, we compared MRI patterns between aCL Ab positive patients and matched aCL Ab negative patients.

METHODS

Patients

From January 1999, we obtained serum samples from 143 consecutive patients who were diagnosed as having definite MS, according to the Poser criteria, or as neuromyelitis optica (NMO, Devic's disease). Blood was drawn after obtaining ethics committee approval and patient informed consent. Disability at baseline and follow-up was assessed according to the Kurtzke Expanded Disability Status Scale.[10]

Assessment of cardiolipin antibodies

All sera were tested for IgM and IgG aCL Ab in a routine diagnostic procedure using an ELISA based on purified cardiolipin (Sigma Aldrich Steinheim, USA). Cofactors, such as β2-glycoprotein I, were provided by a second incubation of the cardiolipin coated plates with newborn calf serum. Results were standardised according to the Harris directives.[11] Values exceeding 10 GPL or MPL units were considered positive. Levels of aCL exceeding 40 GPL or 40 MPL units was considered a laboratory criterion for APS.[3]

Assessment of MRI scans

Routine MRI acquisition was performed at baseline and consisted of pre and post contrast T1 and T2 weighted brain and spinal cord images. MR images were analysed by specialist MS neuroradiologists (ES and FB) who were blinded to the clinical findings and aCL Ab status. MR images were systematically reviewed for MS criteria of dissemination in space and for various abnormalities of presumed vascular origin (see table 2).[12] To assess the MS criteria of dissemination in time, follow-up scans (which were obtained at variable intervals from baseline) were reviewed.

Abbreviations: aCL Ab, anticardiolipin antibody; APS, antiphospholipid syndrome; MS, multiple sclerosis; NMO, neuromyelitis optica; OCB, oligoclonal bands

Table 1 Characteristics of patients with repeated aCL Ab positivity

Patient No)	Sex/ age (y)	Second positive aCL Ab	Clinical course	Disease duration (y)	EDSS	ΔEDSS/y	No of IVMP treatments	CSF IgG index	CSF OCB	No of MRI MS criteria for dissemination in space[12]	APS related symptoms
1	F/40	IgG +	RR	3	1	0.4	1	0.65	No	4	No
2	F/39	IgM +, IgG+	RR	11	2	0.3	4	2.20	–	4	DVT, headache
3	F/35	IgM +	RR	18	4	0.0	2	–	–	0	No
4	F/45	IgG +	RR	11	4	0.2	3	–	–	3	No
5	M/40	IgG +	RR	11	1.5	0.3	10	Increased	No	4	No
6	F/37	IgM +	PP	13	4	0.3	5	1.23	No	4	Headache
7	M/34	IgG +	RR	1	1.5	0.6	6	1.09	1 weak	3	No
8	F/37	IgG +	Devic	<1	3.5	0.3	2	1.10	No	1	No

aCL Ab, anticardiolipin antibody; APS, antiphospholipid syndrome; DVT, deep venous thrombosis; EDSS, Expanded Disability Status Scale; ΔEDSS/year, change in EDSS per year; IgM/IgG+, >10 MPL/GPL units; IVMP, intravenous methylprednisolone; MS, multiple sclerosis; OCB, oligoclonal bands; PP, primary progressive; RR, relapsing remitting.

The MR images of the eight patients with persistent aCL Ab positivity were compared with those of 24 controls, consisting of patients with definite MS but without aCL Ab positivity. The controls were matched for subtype of MS (relapsing–remitting, primary progressive, NMO), sex, age and duration of disease.

RESULTS

Of the 143 patients (45 men and 98 women, mean age 39.3 (SD 10.2) years), 102 (71%) had a relapsing–remitting, 26 (18%) a secondary progressive and 9 (6%) a primary progressive MS disease course. Six (4%) patients had NMO (Devic's disease).

Of the 143 patients, 21 had a positive test for IgM (n = 7), IgG (n = 12) or both IgM and IgG (n = 2) aCL at the first analysis. After the first test being positive, only eight of these 21 patients had a positive test for a second sample. Six of these eight positive second samples were obtained at least 12 weeks later. The other two samples were obtained after 9 and 11 weeks. No sample had aCL Ab levels exceeding 40 GPL or 40 MPL units. An increase in IgG positivity was noted in five second samples with one patient showing additional IgM positivity.

The eight patients with persistent aCL IgM and/or IgG had clinical follow-up of 7 years on average. Their clinical and MR characteristics are given in tables 1 and 2, respectively. None of the repeatedly positive patients fulfilled the criteria for APS, although one patient (patient No 2 in table 1) suffered from deep venous thrombosis and had specific treatment for this indication (anticoagulants).

No statistically significant differences were found in MR characteristics of repeatedly aCL Ab positive compared with aCL Ab negative MS patients (χ^2 test).

DISCUSSION

We found eight of 143 MS patients (5.6%) with aCL Abs on two occasions, with the majority performed at least 12 weeks apart. Although all aCL Ab levels were insufficient to be a laboratory criterion for APS, persistent low positive aCL Ab titres could still represent a separate subgroup of MS. None of the positive MS patients fulfilled the criteria for APS, although one had suggestive clinical symptomatology and therefore had specific treatment (anticoagulants).

We compared MRI features of MS/NMO patients who were aCL Ab positive versus matched MS patients who were aCL Ab negative, specifically focusing on those imaging patterns that are known to discriminate between demyelinating and vascular disease. We were unable to identify any meaningful differences, although it must be recognised that the number of patients might have been too small to detect subtle differences.

Our study is the first to use the updated criteria for definite APS in a large cohort of patients with definite MS. It is also the first that has combined repeated measurements after 12 weeks, long term clinical follow-up and systematic MRI comparison.

Table 2 MRI characteristics of the brain and spinal cord in eight patients with definite MS and persistent aCL Ab positivity, compared with 24 controls with definite MS but with no aCL Ab

Characteristic	aCL Ab positive MS (%) (n = 8)	aCL Ab negative MS (%) (n = 24)
MS criteria for dissemination in space[12]		
≥9 T2 lesions	6/8 (75%)	17/24 (71%)
Gadolinum enhancement	5/8 (63%)	10/21 (48%)
≥1 infratentorial lesion	5/8 (63%)	18/24 (75%)
≥1 juxtacortical lesion	4/8 (50%)	12/24 (50%)
≥3 periventricular lesions	6/8 (75%)	18/24 (75%)
Other		
≥1 black hole(s)	6/8 (75%)	11/22 (50%)
Mean No of lesions	48/6 = 8	52/11 = 5
≥1 infarct-like lesions	0	0
≥1 lacunes	0	0
≥1 basal ganglia lesions	4/8 (50%)	10/24 (42%)
≥1 cortical lesions	0	0
≥1 temporal lobe lesions	3/8 (38%)	14/24 (58%)
Central pontine hyperintensity	0	1/24 (4%)
Signs of past (micro)haemorrhage	0	0
Dissemination in time present	3/4 (75%)	10/15 (67%)
Demyelinating lesion(s) spinal cord	5/5 (100%)	17/18 (94%)

aCL Ab, anticardiolipin antibody; APS, antiphospholipid syndrome; MS, multiple sclerosis.

Studies addressing the relationship between aCL Ab and MS have been conflicting to date. Only two studies reported repeated testing of aCL Ab in MS (two measurements at least 6 weeks apart).[8 9] In a prospective follow-up study, 19 patients were identified who had typical imaging findings of MS and were consistently positive for aCL.[8] It was argued that these patients form a subgroup of MS, because of a slower progression of disease, an association with specific clinical features (myelopathy, optic neuropathy and headache) and absence of oligoclonal bands (OCB) in CSF. A different pathogenesis, involving aCL Ab, was suggested for these patients, but this study has been criticised because patients were preselected regarding their atypical clinical manifestations. A recent study showed that MS patients without OCB in their CSF showed aCL Ab positivity more frequently than OCB positive patients.[13] This is in line with our study, in which of four aCL Ab positive MS patients out of five tested for OCB, bands were absent in CSF.

Our results are in agreement with a study in which 23 patients (14%) of an unselected population (n = 161) of patients fulfilling the criteria of having probable or definite MS were aCL Ab positive.[9] After 5 years of follow-up, a definite diagnosis of MS was established in 50 patients, of whom eight patients were consistently aCL Ab positive. No differences in clinical signs, symptoms or disease course were detected. The prospective nature of this study is appreciated. However, 24% of patients were lost to follow-up, limiting the strength of the conclusions.

To examine the hypothesis that patients with aCL Ab represent a separate subgroup of MS, two studies reported the prevalence of aCL in a large cohort of unselected subjects with definite MS.[14 15] The prevalence of aCL Ab was 2% in one study and 15% in the other. No specific clinical or autoimmune characteristics were present in the positive patients. Again, none of these positive patients underwent repeated tests. Furthermore, both studies lacked a detailed description of MRI characteristics.

In summary, a well balanced conclusion on the role of aCL Ab in MS has been difficult to draw because of the fact that different study designs and definitions of positivity have been applied. Our study failed to link aCL Ab to specific clinical and radiological features in MS. As no patient with definite MS fulfilled the criteria for APS, we found no evidence for misdiagnosis or coexistence of APS in MS.

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