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Lupus Anticoagulant -- A Double Misnomer

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SUMMARY **The clinical features of thirteen Chinese patients with lupus anticoagulant were described. They were noted to conform to those reported among Caucasians and tend to suggest that the term 'lupus anticoagulant' is a double misnomer.**

Lupus anticoagulant is a spontaneously acquired inhibitor of blood coagulation which interferes with the activation of prothrombin by the prothrombin activator complex. Its presence was first described in 1951 by Mueller *et al.,* who reported a patient with an unusual circulating anticoagulant.[1] It was not until 1972 when Feinstein and Rapaport referred to the inhibitor with the term lupus anticoagulant.[2] However, it seems apparent that the term is a double misnomer. Not only more and more patients without systemic lupus erythematosus are being reported to have lupus anticoagulant, it is also clear that although it interferes with the clotting process *in vitro,* most patients with this inhibitor do not have a tendency to bleed *in vivo.*

We report here thirteen Chinese patients in our department with lupus anticoagulant. Their clinical features were found to conform to those reported among Caucasians.

PATIENTS AND METHODS

Thirteen Chinese patients with lupus anticoagulant were studied. Eleven were females and two were males, aged 24 to 64. Only nine of the patients (*i.e.,* patients 1 to 9) satisfied the criteria for the diagnosis of systemic lupus erythematosus as set by the American Rheumatism Association in 1982. Patients 10 to 13 did not have any underlying disease and were otherwise normal individuals.

Antinuclear antibody, venereal disease reference laboratory's slide flocculation test (VDRL) and Treponemal immobilization test (TPI) were done by standard methods. Anti-DNA antibody was detected by the *Crithidia luciliae* test. The presence of lupus anticoagulant was suspected by the prolonged activated partial thromboplastin time not corrected by mixture with normal plasma. Its presence was further confirmed by the tissue thromboplastin inhibition test (*i.e.,* prothrombin time determination with serially diluted thromboplastin reagent). With thromboplastin diluted 1:1000, lupus anticoagulant was accepted to be present when the prothrombin time of the patient was at least 1.3 times the prothrombin time of the control.[3,4] IgG and IgM anticardiolipin antibodies were measured by a double antibody sandwich enzyme linked immunosorbent assay[5] with the kind help from the laboratory of Harris *et al.* at the Hammersmith Hospital, London, U.K. The quantitative normal range was 0-9.0 Hammersmith Anticardiolipin ELISA units (HAEU) for IgG and 0-8.0 HAEU for IgM anticardiolipin antibody.

RESULTS

The major clinical and laboratory features of the thirteen patients are summarized in Table 1.

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Table 1 Clinical features of 13 Chinese patients with lupus anticoagulant

	Patient	Sex	Age	SLE	Thrombosis Art.	Thrombosis Ven.	Fetal loss	Live births	Platelet count (x10⁹/L)	L.A.	Anti-cardiolipin* IgG	Anti-cardiolipin* IgM	False VDRL	CNS S/S	Surgical procedures
1.	FLT	F	39	+	–	–	4	–	27 – 70	+	42	4	–	epilepsy	D & C catheterization
2.	LSF	F	58	+	+	–	–	5	70	+	17	0.8	–	–	renal biopsy aortic bypass graft
3.	LSC	F	38	+	+	+	1	2	163	N/A	122	2.7	–	epilepsy myasthenia gravis	–
4.	LML	F	35	+	–	–	1	–	72	+	13.5	0.7	–	reactive depression	renal biopsy
5.	YTY	F	24	+	–	–	1	1	304	–	10.5	13	–	–	renal biopsy
6.	NK	F	36	+	–	–	N/A	N/A	30 – 80	+	N/A	N/A	+	psychogenic psychosis	left hip replacement
7.	NYK	F	33	+	–	–	3	1	180	+	0.5	22	–	–	D & C renal biopsy
8.	TYK	F	27	+	–	–	N/A	N/A	250	+	13.5	5.3	–	–	renal biopsy
9.	YCS	M	32	+	–	–	N/A	N/A	250	+	0.5	0.2	–	–	renal biopsy
10.	LKS	M	27	–	–	+	N/A	N/A	180	+	32.5	6.4	+	–	–
11.	ES	F	24	–	–	–	N/A	N/A	180	+	0.5	4.8	–	–	–
12.	CH	F	64	–	+	–	–	2	47 – 88	+	270	7.2	–	–	–
13.	TSL	F	31	–	+	+	7	–	75	+	N/A	N/A	+	–	D & C

* Hammersmith Anticardiolipin Elisa Units
L.A. = lupus anticoagulant
Art. = arterial; Ven. = venous
D & C = dilatation and curettage

None of the patients reported any undue bleeding tendencies. Instead, five of them had arterial or venous thrombosis or both. Arterial thrombosis occurred in four patients, resulting in femoral artery occlusion, confirmed by arteriogram in patients 2 and 13 and cerebral infarction, confirmed by computerized axial tomography in patients 3 and 12. In fact, patient 3 developed the cerebral arterial thrombosis while she was already on Warfarin. All the three venous thrombotic episodes involved the deep femoral vein and in patient 3, who developed both arterial and venous thrombosis, recurrence of deep vein thrombosis occurred within one week after stopping the Warfarin.

Eight of the 11 female patients had history of conception. Only five of them managed to give births to live babies. In patients 2, 3 and 12, the babies were born 10 to 30 years before the detection of the lupus anticoagulant. Patients 5 and 7 had successful pregnancies after they were known to have the lupus anticoagulant. They were on Imuran and prednisone for their lupus nephritis at the time of conception. Abortions or intrauterine deaths occurred in six patients, three of whom had 3 or more pregnancies resulting in fetal deaths. In patients 1, 3 and 4, all the abortions were spontaneous and occurred 5-10 years before the patients were diagnosed to have SLE. In patient 5, the abortion was also spontaneous and occurred 4 years after she was diagnosed to have SLE and the disease was under conrol. In patient 7, two of the abortions occurred spontaneously 4 and 5 years before the diagnosis of SLE. One abortion was induced when she became pregnant while her SLE disease was still active. Patient 13, who had the most frequent abortions, did not have any underlying disease.

Persistent thrombocytopenia (platelet count $< 100 \times 10^9/1$) occurred in six patients and among them three (*i.e.*, patients 2, 12 and 13) had thrombotic events.

Lupus anticoagulant was demonstrated in all patients except two. In patient 3, the detection was not possible because she could never

manage to do without Warfarin. In patient 5, the APTT was consistently shorter than that of control on several occasions. Measurement of anticardiolipin antibodies could be arranged in only eleven of the patients. All patients except patients 9 and 11 had significant anticardiolipin antibodies, IgG or IgM or both. Three patients had positive VDRL test at 1:1 dilution but all of them were negative for TPI.

Neurological symptoms were evident in four patients. Patients 1 and 3 had grand mal epilepsy requiring anticonvulsant therapy. Patient 3 also had myasthenia gravis requiring mestinon. Patients 4 and 6 had history of reactive depression and psychogenic psychosis, respectively.

Nine of the thirteen patients had undergone some form of surgical procedure without any bleeding problems. Renal biopsies were performed in patients 2, 4, 5, 7, 8 and 9 in the course of work up for the extent of the lupus involvement. Cardiac catheterization was done for patient 1 in view of her increasing exertional dyspnoea and the presence of a mitral incompetence murmur. Aortic bypass graft had to be done for patient 2 because of her severe ischaemic limb pain. Left hip replacement was done for patient 6 who developed avascular necrosis of the hip. Patients 1, 7 and 13 had dilatation and curettage for abortions.

DISCUSSION

In 1951 Mueller *et. al.*[1] described a SLE patient with an unusual inhibitor of coagulation. A year later Conley *et al.* described 2 other SLE patients with the same problem.[6] In 1955 Frick described a similar inhibitor in an individual who did not have SLE.[7] All four patients had false positive serology for syphilis. Feinstein and Rappaport in 1972 referred to this inhibitor with the term lupus anticoagulant.[2]

Early workers have already noted that although lupus anticoagulant clearly interferes with the clotting process *in vitro,* most patients with this inhibitor do not have a tendency to bleed. Bleeding strictly related to the action of the lupus anticoagulant is a very rare event. When bleeding is present, it can usually be attributed to associated haemostatic defects or causes such as hypoprothrombinaemia, severe thrombocytopaenia, uraemia and qualitative platelet defect. This is well illustrated in our thirteen patients, none of them having any bleeding problems. In fact, nine of them had undergone various surgical procedures without undue bleeding.

In 1963, Bowie *et al.* first described the occurence of thrombotic complications in patients with SLE and lupus anticoagulant.[8] This phenomenon has provoked a lot of interest and has since been recognized by many others. Lechner *et al.* reviewed the literature in 1985 and noted that 85 out of 259 patients having lupus anticoagulant developed thrombosis (*i.e.,* 32.8%).[9] In our series, five of the thirteen patients (*i.e.,* 38.5%) had thrombosis. There is reason to believe that these prevalence figures might be overestimates. There is a great bias favouring patients with thrombotic diseases since many patients with lupus anticoagulant were detected during study of patients with undue thrombotic diseases. Conversely, many asymptomatic patients with lupus anticoagulant remained undetected. However, in a study of > 800 patients with venous thrombotic disease, Lechner and Pabinger-Fasching found lupus anticoagulant in only <2% of them.[9]

The reported prevalence of lupus anticoagulant in patients with SLE varies from 5 to 37%.[10] Higher incidence would be obtained when lupus anticoagulant is specifically sought with the use of more sophisticated techniques. A generally accepted figure is 10%. There is mounting evidence to suggest that SLE patients with lupus anticoagulant may form a clinically distinct subset within the constellation of the multifold findings in SLE in general. Lupus anticoagulant also occurs in nonlupus patients, although it is difficult to establish its prevalence in this group of patients. It may occur in patients with other autoimmune disorders, *e.g.,* polyarteritis nodosa and mixed connective tissue disease, in certain drug induced disorders, *e.g.,* phenothiazines, in patients with malignancy and in otherwise normal individuals. About 1/2 of a large series of 219 patients with lupus anticoagulant did not have SLE or other SLE like disorders.[11] In our series, four of the thirteen patients do not satisfy the criteria for diagnosis of SLE.

One of the striking features of lupus anticoagulant associated thrombosis is the fact that they are obviously associated with an increased tendency towards venous as well as arterial thrombosis. According to most series, deep vein of the leg is the most common site of thrombosis[9] and all the venous thrombosis in our patients occurred in that site. It is interesting to note that patients with lupus anticoagulant have obviously no increased risk for coronary thrombosis. None of our patients had documented myocardial infarction. Only in the report of Wadell and Brown[12] were 4 patients with coronary artery disease mentioned but all those patients were in an age group where coronary artery disease is common anyway.

Explanations for the association between the lupus anticoagulant and thrombosis are open to speculations. Interference with antithrombin III activity[13] and inhibition of the function of human thrombomodulin,[14] the endothelial cofactor in the activation of protein C by

thrombin, have been suggested as possible causes. However, deficiency of antithrombin III and protein C have until now been related to venous thrombosis only. Some workers suggest that lupus anticoagulant may damage blood platelets and increase their adhesiveness, thereby initiating thrombosis.[15] It is noted that thrombocytopaenia is a common finding in patients with lupus anticoagulant. In our series, three of the five patients with thrombotic problems had persistent thrombocytopaenia. The possibility that thrombosis may be linked with inhibition of prostacyclin production has been suggested by many studies.[16-18] More recently, some workers suggest that development of antiidiotypic antibody to lupus anticoagulant may be a possible mechanism.[9] In view of the accepted heterogeneity of lupus anticoagulant, it is likely that different mechanisms may be involved in the development of thrombosis in different patients.

In 1975, Nilsson described a patient with lupus anticoagulant and recurrent abortions.[19] In 1980 Soulier and Boffa described three patients with recurrent abortions, thrombosis and lupus anticoagulant.[20] It is fairly widely recognized now that in women with or without SLE, presence of lupus anticoagulant is associated with high incidence of first trimester abortions and second and third trimester fetal deaths. Six of our patients had histories of spontaneous abortions and in two of them thrombotic events occurred as well. All of these patients except patient 13, who had the greatest numbers of abortions, satisfied the criteria for diagnosis of SLE. In fact a syndrome of thrombosis, recurrent abortions and presence of lupus anticoagulant in females who do not have other serological features for lupus is gradually being delineated. Patient 13 is a classical example of such a syndrome.

In the literature only two women in whom lupus anticoagulant was discovered before conception or early in pregnancy and who did not receive any treatment have been reported to have given birth to live infants. Both required preterm delivery because of severe preeclampsia or placental insufficiency. Five of our patients had given birth to live infants. However, in three of them, the successful pregnancies occurred 10, 20 and 30 years before the detection of lupus anticoagulant. It is most likely that the lupus anticoagulant might not have been present then. In the other two patients, they were on Imuran and prednisone for their lupus nephritis when they were pregnant. Both medications have been shown to be useful in preserving pregnancies in patients with lupus anticoagulant.[21,22]

Since early days it has been recognized that there is an association between lupus anticoagulant and false positive VDRL. The proportion of patients with positive VDRL is greater in those patients with history of thrombosis. This is not surprising since cardiolipin itself is a negatively charged phospholipid with which an antiphospholipid antibody could react. In recent years, highly sensitive techniques for detection of anticardiolipin antibodies have been developed, *e.g.* radioimmunoassay and ELISA.[23] There appears to be a good correlation between presence of lupus anticoagulant and anticardiolipin antibody as measured with these sensitive methods. In our series, only 3 patients had a false positive leu serology. There is a good correlation between the presence of lupus anticoagulant and anticardiolipin antibody. In patient 5, although lupus anticoagulant was not demonstrated by the thromboplastin dilution test, she was detected to have a fairly significant level of anticardiolipin antibody. This is in keeping with the fact that the measurement of anticardiolipin antibody is a more sensitive method than the thromboplastin dilution test in the detection of lupus anticoagulant.

The foregoing discussion makes it apparent that the term lupus anticoagulant is a double misnomer. It has been suggested that the term could be replaced with the term 'anti APTT' coagulant protein.[17] However, the latter term appears too restrictive regarding abnormalities in other clotting tests and more importantly, it ignores the strong clinical association with SLE. Thus, until the lupus anticoagulant can be defined in more precise biochemical and functional terms, it would appear better to retain the term 'lupus anticoagulant' even with the full recognition that its *in vivo* role is not primarily to retard haemostasis.

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