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Systemic lupus erythematosus

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Summary: Systemic lupus erythematosus is a common disease – studies throughout the world broadly agree on a prevalence of 1 in 1000 women.

Recently an important clinical advance has come from the description of a syndrome of recurrent thrombosis, recurrent abortion and neurological disease associated with antiphospholipid antibodies. The discovery that immunological mechanisms may apply in some cases of thrombosis has led to new insights into the aetiology and treatment of vascular disease in general.

Introduction

This paper reviews briefly some aspects of systemic lupus erythematosus (SLE) of current interest, including its epidemiology, genetics and immunological abnormalities. The existence of clinical subsets of SLE is highlighted.

Epidemiology

Twenty years ago, systemic lupus erythematosus was widely regarded as a rare disease. Centres publishing series of 100 or more patients could be counted on two hands. Now, lupus is recognized as a major cause of illness throughout the world, with prevalence figures as high as one in 2000. Indeed, in certain countries in the Far East, including China, lupus may be overtaking rheumatoid arthritis as the major connective tissue disease.

It has commonly been stated that the prevalence is greater in certain ethnic groups (for example in Black and in Chinese women) though epidemiological studies depend heavily on diagnosis. For example, until a decade ago, lupus was thought to be rare in the continents of India and Africa, the latter in marked contrast to its high prevalence in the West Indies. Although no detailed figures are available, it is now known that these impressions were untrue.

Lupus is predominantly a disease of young women, its peak onset being between 15 and 40. This may contribute to the high incidence in 'developing' high population countries. Furthermore, it is obvious that socio-economic factors must influence the pattern of disease, with late presentation (e.g. with advanced renal disease) being commoner in poorer countries, and poorer groups in general.[1]

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Is lupus on the increase? It seems sensible to attribute the huge increase in SLE numbers to improved diagnosis. The main diagnostic advances in SLE have all been recent – the LE cell test in 1948, the ANA in 1957, DNA antibody tests in 1966–69, and anti-cardiolipin testing in 1983–84. Furthermore, the genetic hypothesis for the aetiology argues against a true massive increase.

Nevertheless, the increase is striking, and changes in possible environmental factors may yet prove significant. For example, for debate, it would be interesting to know the effects of a 40% decrease in the protective ozone layer of the atmosphere[2] on the rate of appearance of a disease such as lupus characterized as it is by UV light sensitivity.

Genetics

A number of studies have shown an association with the HLA B8 DR3 haplotype.[3] Furthermore, an association with a C4 null allele has been demonstrated.[4] The latter is in strong linkage disequilibrium with B8 DR3 and international studies are in progress to determine the relevance of the latter finding. Again, HLA studies depend on clinical definition. For example, there may be a stronger association of B8 DR3 with subacute cutaneous LE,[5] and in drug-induced lupus, a separate clinical entity, the association is with HLA DR4 (together with female sex and slow acetylator status).[6] In the antiphospholipid syndrome, there may also be an association with C4-null containing haplotype (Dr Wilson, personal communication).

Lupus has always been associated with complement deficiencies with Gm allotypes, and (though this is disputed) with CR1 receptor deficiencies. The significance of these findings is reviewed by Winchester and Lahita.[3]

Such studies largely serve to confirm early clinical observations of an increased familial (and twin) tendency in SLE. All of us who have carried out large family studies in this disease confirm the finding of an increased prevalence of autoantibodies (notably ANA and ENA) in relatives and offspring of SLE patients, suggesting that clinical disease expression occurs in only a minority of susceptible individuals.

Autoimmunity

It is an over-simplification to regard SLE simply as a defect in suppressor T cell function resulting in an across-the-board over-production of autoantibodies. The clinical spectrum of SLE has thrown up some interesting observations. For example, despite the tendency to produce polyclonal B cell activation, certain autoantibody patterns show through. In typical SLE for example, the antibodies are largely directed against non-organ-specific (nuclear or cytoplasmic) antibodies. Although most textbook chapters also list organ-specific (anti-thyroid, etc.) antibodies in the SLE spectrum, this may not be the case. One recent survey of over 1000 SLE sera in fact showed that organ-specific antibodies were distinctly uncommon (Dr Evelyn Hess, personal communication).

Other interesting antibody-disease patterns are the association of anti-Ro (often ANA negative) with subacute cutaneous LE and with heart block, the serological pairing of anti-Ro/anti-La and anti-RNP/anti-Sm, and the striking association of anti-phospholipid antibodies with thrombosis – often in the absence of any other demonstrable autoantibodies. Perhaps the most tantalizing syndrome is the much-maligned mixed connective tissue disease – a relatively distinct syndrome with severe Raynaud's and arthritis, in which one antibody (anti-RNP) is present, sometimes in enormous proportions.

Hormonal

Sex hormones have important effects on the immune response.[7] Androgens, for example, appear to modulate thymocytes in their transition from marrow to thymus, and may well have an immunosuppressive effect. Interesting studies in the NZB/NZW mouse, in which the female has a high predilection to lupus, have shown that oestrogen therapy accelerates the disease in females. Likewise, in the MRL strain, some evidence suggests that testosterone delays the development of autoimmune disease.

In human SLE, a number of clinical and other observations have suggested that hormonal factors influence the disease (Table I). In the prepubertal and post-menopausal years, the sex ratio is nearer equality, whilst in the early 20s, the female:male ratio may be as high as 30:1. Perhaps the most interesting data linking sex hormones with SLE disease expression has come from the Rockerfeller University and other centres, where it has been found that some females with SLE had altered metabolism of sex hormones with increased shunting to hydroxylated oestrogen.[7]

Table I Evidence for hormonal mechanisms in SLE

F:M Ratio 9:1
Pre-menstrual exacerbation
Klinefelter's syndrome and SLE
Occasional exacerbation by oestrogens
Studies in NZB/W and other mouse models

Disappointingly, the experimental data have not as yet resulted in direct therapeutic benefit. A number of attempts at the use of danazol, especially in women with pre-menstrual exacerbation, have had mixed results.

Antibodies in SLE

Table II lists the prevalence of anti-nuclear and anti-cytoplasmic antibodies in a series of 1000 patients with SLE and related diseases. Anti-DNA antibodies (preferably assayed by Farr technique) have stood the test of time in the diagnosis of SLE. Anti-Sm antibodies, though relatively specific for SLE, are found in only a minority of our patients. Our data suggested that anti-Sm antibodies were more frequent in Chinese and Black patients, though this has yet to be confirmed.

Levels of anti-DNA antibodies serve as a rough and ready guide to disease activity. It has been suggested that levels of these antibodies are, in turn, influenced by anti-idiotypic antibodies. In a interesting series of animal experiments Dr Bevra Hahn and colleagues demonstrated suppression of anti-DNA antibodies and a delay in the onset of nephritis in NZB/W mice by administration of syngeneic monoclonal anti-DNA antibody, resulting in the production of anti-idiotypic antibodies.[8]

Clinical features

The clinical features of classical SLE are well known and will not be rehearsed here. Perhaps the main trends of the past two decades have been, firstly, the realization that in most patients the disease ultimately goes into remission – normally at

Table II Disease associations in 1018 sera from different connective tissue diseases. The most important are italicised

Antibody system	*Disease*								
	SLE	*MCTD*	*Primary Sjögrens syndrome*	*Myositis*	*PSS*	*RA*	*PBC*	*CAH*	*Other*
Sm	7	7	—	—	—	—	—	—	—
RNP	23	*100*	4	14	2.5	—	—	—	—
Ro	24	17	*75*	8	4	3	6	4	—
La	8	3	42	—	—	—	—	—	—
Jo-1	—	3	—	*25*	—	—	—	—	—
SL	6	3	—	—	—	—	—	—	—
Pm-Sci	—	—	—	11	—	—	—	—	—
XR	—	—	—	—	—	—	10	11	—
SCL-70	—	—	nd	—	16	—	nd	nd	—
Centromere	2	—	—	—	29	—	8	—	—
Mitochondria	—	—	4	—	—	—	*88*	2	—

Taken from Hughes, G.R.V. *Br Med J* 1984 **289:** 339–442, which was modified from Bernstein R.M., Bunn & Hughes, G.R.V., *Mol Biol Med* 1984, **2:** 105–120, with permission of the publishers. MCTD – mixed connective tissue disease; PSS – systemic sclerosis; RA – rheumatoid arthritis; PBC – primary biliary cirrhosis; CAH – chronic active hepatitis.

or after the menopause. This has, to a large extent, resulted in a more conservative approach to therapy.[9] The second has been the recognition of the frequency and importance of central nervous system (CNS) features. Rarely nowadays is the old sore of 'steroid psychosis' raised at the bedside. In a patient with SLE and a behavioural or psychiatric problem, the aetiology is (statistically at least) almost certainly related to the underlying disease. The fact that, in some SLE patients, neuropsychiatric flares can exist in a period of otherwise disease and serological quiescence, leads one to speculate on the number of cases of 'idiopathic' psychiatric illness that might have been thus missed.

Clinical sub-sets

Pre-lupus

Ask the average 25 year old patient first diagnosed with SLE whether she had 'growing pains' as a teenager? Yes doctor. Or atypical 'rheumatic fever'? Yes. Or recurrent migraines? Frequently. Or prolonged 'glandular fever'? Yes. Or even exaggerated skin reactions to insect bites and stings?

Family studies, as mentioned, have shown that subclinical immune abnormalities may be present in asymptomatic relatives and offspring of SLE patients. Clinically, retrospective questioning very frequently elicits a history of childhood and teenage symptoms which could well be interpreted as 'pre-lupus'. Another SLE feature which may antedate other disease expression is epilepsy. In our clinic the prevalence of epilepsy prior to diagnosis in SLE patients was eight times the national figure. Clinical observations such as these may contribute to the wider recognition of SLE, though it is debatable whether they would alter current approaches to therapy.

Anti-Ro disease

The anti-ENA anti-Ro is an important clinical test. It has helped to define a number of clinical subsets of SLE (see Table III).

ANA-negative lupus is a loose clinical term which has come to be associated with a triad of mild disease (nephritis is rare), sicca syndrome and a marked propensity to skin rashes and photosensitivity. The antigen Ro is predominantly cytoplasmic, thus providing a simplistic reason for the negative conventional ANA test in many of these patients.

Dermatologists have long recognized a clinical variant of SLE, subacute cutaneous LE, somewhere intermediate between SLE and discoid, with erythematous or annular lesions on the face, arms and trunk. Systemic features are mild. Up to three quarters of these patients are HLA DR3.

Table III Associations of anti-Ro

ANA negative lupus (anti-Ro found in 2/3)
Primary Sjögren's syndrome
Subacute cutaneous LE (SCLE)
C2 deficiency
Neonatal lupus
Congenital heart block
Photosensitivity

Neonatal lupus

Rarely, offspring of SLE mothers develop a lupus-like rash, occasionally associated with splenomegaly and lymphadenopathy and other LE features. The sera of these infants have antibodies to Ro, thought to have crossed the placenta. Both the antibodies and the clinical features disappear spontaneously within 6–8 months.

Congenital heart block

This is a rare abnormality found in the offspring of SLE patients. In studies of the mothers of children with congenital heart block, up to 80% of the mothers have anti-Ro antibodies. It has been suggested that transplacental passage of anti-Ro might directly contribute to the heart block, possibly through myocarditis. It is possible that the antibody fixes directly to Ro antigen, itself concentrated in heart conducting tissues. However, this is, at best, speculative. The vast majority of individuals with circulating anti-Ro (including 23% of our SLE patients) have normal offspring.

Drug-induced lupus

The true prevalence of drug-induced lupus is hard to assess, though it is probably rare. When cases of lupus-like disease were first reported in association with procainamide, hydralazine and other drugs, speculation arose that such cases might provide clues to triggering factors in SLE (e.g. tartrazines, etc.). The syndromes are very different.[10] Drug LE classically regresses on drug withdrawal, the association may be with HLA DR4, and the autoantibody profile is different. Anti-histone antibodies (and generally negative anti-ENA profiles) have been found in some cases, but as yet have failed to contribute usefully to clinical dissection of various drug LE syndromes.

The antiphospholipid antibody syndrome

The earliest known antibody in SLE is the Wasserman reaction. Antibodies against phospholipids such as Wasserman reagent and the confusingly named 'lupus anticoagulant' have been observed in a small number of SLE patients. Although a lupus anticoagulant might theoretically be associated with a bleeding tendency, this was never shown to be the case. In fact sporadic cases of thrombosis were reported. In 1983 and 1984, having confirmed a strong association between the lupus anticoagulant and thrombosis (including placental thrombosis) we devised a sensitive immunoassay for antiphospholipid antibodies, using the readily available antigen cardiolipin.[11,12] It has become apparent to us that high titres of anticardiolipin antibodies are associated with a distinct syndrome – separate from SLE, and characterized by recurrent venous and arterial (especially cerebral) thrombosis, recurrent placental thrombosis and abortion, as well as other features.[11–13] (Table IV). We have chosen to call this syndrome the anticardiolipin syndrome or, more correctly, the antiphospholipid antibody syndrome. The reasons for the thrombosis are uncertain – two possible mechanisms suggested are through an action on the negatively charged phospholipids on platelet membranes, or on endothelial cell membranes.

For us, this aspect of our work on SLE has been rewarding and even exciting. We feel that the increasing numbers of patients with 'idiopathic' coronary, cerebral, and other visceral thrombosis, now being seen in whom antiphospholipid antibodies are detectable, points to their widespread importance across the board in medicine, surgery and obstetrics.

In lupus, the description of this syndrome has filled in yet another blank in the definition of an 'atypical' subset of patients – often DNA-antibody negative – who present with non-inflammatory, but nevertheless disastrous thrombotic disease.

Table IV The antiphospholipid antibody syndrome

1. Thrombosis
Venous
Recurrent DVT (also axillary, IVC and retinal vein thrombosis)
Arterial
Cerebrovascular accidents
Peripheral arterial gangrene
Coronary thrombosis
Retinal artery thrombosis
Other
Pulmonary hypertension
? Avascular necrosis
2. Abortion
Recurrent IUD, placental thrombosis and infarction
3. Thrombocytopenia
Intermittent, often acute
4. Other occasional features
Coombs' positivity
Livedo reticularis
Migraine
Chorea
Epilepsy
Chronic leg ulcers
?Endocardial disease
?Progressive dementia due to repeated cerebrovascular thromboses

(From Hughes *et al.*)[13]

In obstetrics, the identification of a risk factor in a group of patients with recurrent abortion has pointed towards specific modes of treatment, including various anticoagulant regimes, and these are now under trial in centres throughout the world. In immunology, we may be seeing evidence which directly links an immunological mechanism with thrombosis.

But most tantalising of all, in neurology, we are beginning to see cases of multi-infarct dementia associated with these antibodies,[14] suggesting at least one mechanism in this condition.

References

1. Ginzler, E. & Berg, A. Mortality in SLE. *J Rheumatol* 1987, **13**(suppl): 218–222.
2. Russell-Jones, R. Ozone depletion and cancer risk. *Lancet* 1987, **ii:** 443–445.
3. Winchester, R.J. & Lahita, R.G. Genetic susceptibility to systemic lupus erythematosus. In: Lahita, R.G. (ed) *Systemic Lupus Erythematosus:* John Wiley, Chichester, 1987, pp. 81–118.
4. Fielder, A.H.L., Walport, M.J., Batchelor, J.R. *et al.* Family study of the major histocompatibility complex in patients with SLE: importance of null alleles of C4 and C4B in determining disease susceptibility. *Br Med J* 1983, **286:** 425–429.
5. Bell, D.A. & Maddison, P.J. Serologic subsets in SLE: an examination of autoantibodies in relationship to clinical features of disease and HLA antigens. *Arthritis Rheum* 1980, **23:** 1268.
6. Batchelor, J.R., Welsh, K.I., Tinoco, R.M. & Hughes, G.R.V. Hydralazine-induced systemic lupus erythematosus: influence of HLA DR and sex on disease susceptibility. *Lancet* 1980, **i:** 1170–1179.
7. Lahita, R.G. (ed) Sex and age in SLE. In: *Systemic Lupus Erythematosus.* John Wiley, Chichester, 1987, pp 527–540.
8. Hahn, B.H. & Ebling, F.M. Suppression of NZB/NZW immune nephritis by administration of a syngeneic monoclonal antibody to DNA. Possible role of anti-idiotypic antibodies. *J Clin Invest* 1983, **71:** 1728.
9. Hughes, G.R.V. The treatment of SLE: The case for conservative management. *Clin Rheum Dis* 1982, **8:** 299–313.
10. Hess, E. (ed) Drug induced lupus. *Arthritis Rheum* **24:** 979–1108.
11. Hughes, G.R.V. Thrombosis, abortion, cerebral disease and the lupus anticoagulant. *Br Med J* 1983, **287:** 1088–1089.
12. Harris, E.N., Gharavi, A.E., Boey, M. & Hughes, G.R.V. Anticardiolipin antibodies: detection by radio immunoassay and association with thrombosis in SLE. *Lancet* 1984, **ii:** 1211–1214.
13. Hughes, G.R.V., Harris, E.N. & Gharavi, A.E. The anticardiolipin syndrome. *J Rheumatol* 1986, **13:** 486–489.
14. Asherson, R.A., Mercey, D., Phillips, G., Harris, E.N. & Hughes, G.R.V. Recurrent stroke and multi-infarct dementia in SLE: association with antiphospholipid antibodies. *Ann Rheum Dis* 1987, **46:** 603–611.