SYSTEMIC LUPUS ERYTHEMATOSUS

Version 2 Final

Document control

Version history

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Changes since last version

1. Introduction

Systemic lupus erythematosus (S.L.E.) is a chronic, multisystem, inflammatory disorder of autoimmune aetiology, occurring predominantly in young women.
(It is sometimes referred to as Disseminated Lupus Erythematosus) [1]

Description

Systemic lupus erythematosus is an inflammatory multiorgan disease characterised by its clinical manifestations and the occurrence of antibodies against nuclear antigens. The spectrum of clinical manifestations in S L E is wide ranging from mild symptoms to loss of organ function and fatal complications. The course of the disease is characterised by periods of remission and relapse (flares), and much of the current management is directed towards predicting and therefore preventing the flares of disease activity. [2]

SLE may be precipitated by currently unknown environmental triggers that cause autoimmune reactions in genetically predisposed people.
Some drugs (eg, hydralazine, procainamide, or isoniazid) can cause a reversible lupus-like syndrome.

Prevalence

SLE occurs worldwide and estimates of its prevalence have risen over the last 30 years with increased awareness and diagnosis of less severe disease resulting in a worldwide rise in reported cases.
Current best estimates suggest 50 in 100,000 in the USA, 39 in 100,000 in Sweden and 12 in 100,000 in Great Britain. [3]

Of all cases, 70 to 90% occur in women (usually of child-bearing age). It can affect patients of any age, including neonates.
It is at least three times more common in African-Caribbean people, and about twice as common in those of Asian descent as in European Caucasians.

This helps to explain apparent anomalies in quoted incidence and prevalence rates, and prevalence rates of between 1 in 750 and 1 in 250 refer to females in the childbearing (15 – 45) year age group. [4], [5]

The incidence rates show a female : male ratio of 9 : 1.

2. Aetiology

The exact patho-aetiology of systemic lupus erythematosus (SLE) remains elusive. An extremely complicated and multifactorial interaction among various genetic and environmental factors is probably involved.
Multiple genes contribute to disease susceptibility. The interaction of sex, hormonal milieu, and the hypothalamo–pituitary–adrenal axis modifies this susceptibility and the clinical expression of the disease.
The loss of immune tolerance, increased antigenic load, excess T cell help, contribute to B cell hyperactivity and the production of pathogenic autoantibodies.
Finally, certain environmental factors are probably required to trigger the disease. [6]

Genetic
The concordance of SLE in identical twins (25%), dizygotic twins (2%) and the increase in frequency of SLE among first degree relatives, and the increased risk of developing the disease in siblings of SLE patients reflects a polygenic inheritance of the disease. [7] Many different genes contribute to disease susceptibility.

Population studies reveal that the susceptibility to SLE involves human leucocyte antigen (HLA) class II gene polymorphisms. An association of HLA DR2 and DR3 with SLE is a common finding in patients of different ethnicities, with a relative risk for the development of disease of approximately two to five. It is estimated that at least four susceptibility genes are needed for the development of the disease. [6]

Immunological
The most important immunological feature is the production of autoantibodies directed against several antigens, in particular nuclear antigens. Anti-double stranded DNA is found in 70% of patients with lupus, but only 0.5% of patients with other autoimmune diseases eg. Rheumatoid arthritis. Many other autoantibodies are also implicated, some of which are shown in table 1. [8]

Antibody	Frequency	Associations
ANA (Anti-nuclear antibody)	96% - 99%	
Anti-DNA (antibody to native DNA in abnormal titre)	40% to 90%	clinical association with nephritis
Anti-Sm (Sm being an abbreviation for the surname of the patient the antibody was first discovered in)	10% to 30%	nephritis and neuro-psychiatric involvement

Ribosomal P antibody	10% to 20%	Psychosis
Antiphospholipid antibodies	approximately 20%	problems of thrombosis and miscarriage
NMDA receptor	33-50%	Brain disease [9]
Anti-Ro	30-40%	Skin, kidney and foetal heart disease [10]
Anti-C1q	40-50%	Kidney disease [11]

(For further information see Differential Diagnosis – Primary AntiPhospholipid Syndrome.) [12]

Environmental
Certain environmental factors are probably required to trigger the disease.

Chemical/physical factors
- Ultraviolet light (especially UVB, is an important trigger in many patients with SLE.)
- Aromatic amines
- Hydrazines
- Drugs (procainamide, hydralazine, chlorpromazine, isoniazid, phenytoin, penicillamine) – usually present with skin and joint manifestations, renal and neurological symptoms are rare
- Tobacco smoke (which contains hydrazine)
- Hair dyes

Dietary factors
- L-canavanine (alfalfa sprouts)
- High intake of saturated fats
- Vitamin D deficiency [13]

Infectious agents
- Bacterial DNA/endotoxins
- Epstein–Barr virus (EBV) has been strongly implicated- 99% of patients have EBV antibodies and 100% have EBV DNA [14]

Hormones and environmental oestrogens
- Hormonal replacement therapy, oral contraceptive pills
- Prenatal exposure to oestrogens [15]

While many of the above agents have been reported in various publications there is as yet no firm evidence of their individual role although they appear to contribute to the multifactorial interaction.

3. Clinical Features

Fatigue

Overwhelming fatigue is the major reported complaint of patients with stable SLE. This is often related to repeated periods of rest enforced by disease flares. An eight week aerobic conditioning programme was found to decrease the fatigue commonly experienced by SLE patients [16].

Skin and hair

The characteristic clinical feature is the malar (butterfly) rash on the face, although this only occurs in one third of patients. This often occurs after UV exposure and tends to be short lived. UVB light can induce a rash in 60% of patients. The cause is multi-factorial and includes UV damage to DNA.

Apart from the malar rash, two other rashes are commonly seen in SLE. Discoid lupus erythematous is often found around the ears, face, upper parts of the trunk and proximal limbs. Discoid lesions are discrete and annular with slightly infiltrated plaques which extend at the inflammatory periphery leaving depressed central scarring with telangiectasia and de-pigmentation.

Subacute cutaneous lupus is a non scarring lesion which occurs on sun-exposed areas of the face, upper trunk and forearms. It presents as a firm, erythematous maculopapular lesion.

Alopecia occurs in 70% of patients. This is usually non-scarring unless it is due to discoid lesions

Joints

Non-erosive polyarthritis is one of the most common features with 90% of patients affected. It is the presenting feature in 34%. Usually, joint symptoms are transient with swelling, frequently affecting the hands (metacarpophalangeal (MCP) and interphalangeal (PIP) joints), wrists and knees. Occasionally, a more deforming variant may exist, leading to joint deformities similar to those seen in rheumatoid arthritis (RA). Ulnar drift or swan-neck deformities without bony or cartilaginous erosions are known as Jacoud's arthropathy. Although the tendon sheaths in the hands can be involved and cause deformity most patients with lupus have full hand function.
Differentiation from RA may be difficult. SLE arthropathy is usually more migratory and asymmetric, with a greater affinity for the finger PIP joints, as opposed to RA which is more symmetrical and is found most commonly at the MCP joints. Deformity in SLE is due to ligamentous laxity and muscle imbalance rather than the destructive synovitis seen in RA. [17]

Kidneys

Lupus nephritis is found in 50% of cases and can vary from a focal, benign, glomerulitis to a diffuse membranoproliferative glomerulonephritis. Almost all patients with SLE have some histological abnormalities.
Patients with mild mesangial proliferation may have proteinuria while those with focal proliferative through to diffuse proliferative nephritis show increasing impairment of renal function and immune function. Membranous nephritis typically presents with nephrotic syndrome.
Those who progress to end stage renal disease are treated with dialysis or renal transplantation.
Survival rates with either haemodialysis or continuous ambulatory peritoneal dialysis have been reported as greater than 80%.
With transplantation the 1-year graft and patient survival rates were 83% and 98%, and the 5-year graft and patient survival rates were 69% and 96%.
Transplantation has been shown to result in less active disease, as measured by frequency and severity of flare ups. [18]

Central nervous system

Neurological complaints include migraines headache, convulsions, movement disorders, peripheral neuropathies and transverse myelopathies.

A range of psychiatric disorders may be seen in association with SLE.
Patients with inactive or mildly active disease and no overt CNS involvement exhibit symptoms of mild anxiety and depression probably resulting from psychological and social stress rather than from CNS-SLE. By contrast, some patients, particularly non-white Caucasians or those with other systemic or CNS features of active SLE, may demonstrate major depressive illness or psychosis.
Overall, psychiatric symptoms are common in SLE but psychiatric illness severe enough to merit treatment is much less common and psychosis is rare [19].

Cognitive impairment, as demonstrated by psychometric testing, has been found in 20% to 80% of patients with SLE. However it is not progressive in the majority of patients and may fluctuate or resolve without specific treatment.
Cognitive impairment in patients without overt CNS-SLE may result from generalised disease activity of psychiatric disorder which reduce speed, concentration and motivation.

Stroke syndrome (either the result of an embolic process due to anticardiolipin syndrome or a vasculitic process) may result in permanent damage.
Brain CT scans in SLE patients have demonstrated cerebral atrophy and infarcts in more than half of the patients scanned. [20]

Seizures have been reported by 15% of patients with SLE. They are usually of the grand mal type, although petit mal, focal and temporal lobe epilepsy have been reported. They may remain as chronic problems, even when the inflammatory process is no longer present. Although they can be controlled in most cases continuing anticonvulsant therapy may be required.

Eyes

SLE may affect the eyes, optic nerves, as well as the ocular central nervous system. Symptoms include dryness (60%), pain and loss of vision. The retina may be involved in 3-29% of patients and may result in cotton wool spots, intraretinal haemorrhage, vascular tortuosity and aneurysm, and oedema and exudate formation. Severe vaso-occlusive retinopathy is rare, but may result in severe loss of visual acuity. [21]

Cardiovascular system

Accelerated atherosclerosis is an increasing cause of morbidity and mortality in SLE and this may be compounded by the prolonged use of prednisolone. A prevalence of 8% for coronary artery disease, as defined by angina or myocardial infarction, has been reported along with a rate of 40% for hypertension requiring treatment. [22] 34% women under the age of 50 were found to have atherosclerotic plaques in their carotid arteries.[23]

The differential diagnosis of congestive heart failure or low cardiac output in a patient with SLE includes cardiac tamponade (due to pericardial effusion) and myocarditis, but the condition is usually due to atherosclerosis and coronary artery disease.

Pleuropericarditis occurs at some stage in approximately 50% of patients with SLE. Typically the pain occurs in the absence of physical signs, and chest X-ray evidence of pericardial effusions in some patients.

Immune complex deposition in post-capillary venules produces urticaria and vasculitis of small arteries and micro-infacts of the fingertips and toes.

Secondary Antiphospholipid Syndrome (SAPS) causes an increased rate of arterial and venous thromboses, as well as foetal loss. These clinical events are associated with antibodies against cardiolipin and other phospholipids. The vascular occlusion associated with these antibodies differs from the inflammatory vasculitis described above and prevention of recurrent thrombosis in APS is based on the use of anticoagulant rather than immunosuppressive drugs. Although 30 – 40% of those with SLE have antibodies, only 10% are estimated to have SAPS. [24]

Thrombocytopenia is a common feature, usually due to anti-platelet antibodies with a hypercellular marrow and the spleen the major site of platelet destruction. 15% of patients diagnosed with ‘idiopathic’ thrombocytopenic purpura will eventually develop lupus.

Respiratory system

Repeated episodes of pleurisy and pleural effusions can be treated with analgesics (including non-steroidal anti-inflammatory agents) and corticosteroids.The prognosis will relate to the response to treatment and the length of time it takes.
Pleural effusions may also clear by themselves with time.
Restrictive lung disease and lung fibrosis will gradually worsen and the effects are permanent. [3]

Systemic lupus erythematosus is associated with an increased risk of venous and arterial thromboembolism. Acquired or inherited thrombophilic defects were frequently demonstrated in patients with SLE.
Primary thromboprophylaxis should be considered, particularly in patients with SLE with a combination of lupus anticoagulant (LA) and / or anticardiolipin antibodies (ACAs) and factor V Leiden or the prothrombin G20210A mutation. [See also section 6 – severe disease]

4. Investigations

The test most commonly used is the Anti-Nudear Antibody (ANA) test. However this can be positive in other rheumatic diseases and in some healthy individuals. Depending on clinical findings and assessment other blood and urine tests, X-rays and biopsies may be appropriate.

Blood Tests

Over 90% test positive for antinuclear antibodies

SLE patients may have a raised level of Double- Stranded DNA and positive testing for antibodies to double-stranded DNA demonstrates a high likelihood of SLE (but the absence does not exclude it). It can be a useful indicator of disease activity.

40% of those with SLE are Rheumatoid Factor positive.

Other blood tests are necessary to check red blood cells, white blood cells and platelets (to see if there is a reduction in levels).

More specialised testing is available in some laboratories to look for other abnormalities such as testing for C1q antibodies (a feature of lupus nephritis), or autoantibodies, especially DNA, Sm, Ro (an anticytoplasmic rather than antinuclear antibody).

Blood tests to identify the presence of antiphospholipid antibody, which may or may not be present.

Serum creatinine and eGFR (Glomerular Filtration Rate) to assess the level of kidney function. It is raised if kidney function is affected.

Urinalysis

Urine tests are performed to establish the presence of red cells, casts or protein in the urine, which may establish the presence of early kidney disease.

More specialist investigation would involve a 24-hour urine collection.

5. Classification and diagnosis

Classification criteria

Due to a wide range of clinical patterns in SLE, a subcommittee of the American Rheumatism Association produced a list of 14 criteria, in 1971, the presence of four of which would satisfy the disease label of SLE.
The criteria were reviewed in 1982 and modified to the Revised 1982 ARA criteria.
Eleven criteria were defined which allow the identification of SLE with a sensitivity of 97% and a specificity of 98%.
In 1997, the immunologic disorder criterion was revised by a committee. [25]
Some experts consider that the ACR classification blurs the line between diagnosis and classification and would welcome a review.
Currently SLE is considered present if a patient fulfils 4 or more of the 11 criteria. [26]

Criteria	Description
malar rash	fixed erythema, flat or raised, over the malar eminences
discoid rash	erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
photosensitivity	
oral ulcers	includes oral and nasopharyngeal. observed by physician
Arthritis	nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion
Serositis	pleuritis or pericarditis, or evidence of pericardial effusion
renal disorder	proteinuria (> 0.5 g/d, or > 3+) or cellular casts
neurologic disorder	seizures without other cause or psychosis without other cause
hematologic disorder	hemolytic anemia, leukopenia (< 4,000 per µL), lymphopenia (< 1,500 per µL) or thrombocytopenia (< 100,000 per µL), in the absence of a causative drug
immunologic disorder	positive LE cell preparation, anti-ds DNA antibody, anti-Sm antibodies, false positive VDRL
antinuclear antibodies	abnormal ANA titer at any point of time in the absence of drugs known to induce ANA

Differential diagnosis

SLE is a notoriously difficult diagnosis to make. Many patients go for years without diagnosis, and other patients are misdiagnosed as having SLE.

Rheumatoid arthritis

The typical peripheral polyarthritis of SLE is similar to that seen in early rheumatoid arthritis, but on close examination it can be seen that the deformities are due to loosening of the joint capsules and tendons rather than destruction of the articular surfaces of joints. 90% of people with rheumatoid arthritis have a positive rheumatoid factor (with a titre greater that 1:160.

Chronic fatigue syndrome

Constitutional symptoms, especially of severe fatigue may be the presenting complaint and can cause confusion with chronic fatigue syndrome (CFS). Both CFS and viral infections can be associated with low titre anti-nuclear antibodies, which may result in patients being wrongly diagnosed as having SLE.

Fibromyalgia

Usually seen in women and presents with joint and muscle aches. ANA may be present in 15%.

Primary Antiphospholipid syndrome (APS or Hughes Syndrome)

This is a disorder characterized by recurrent venous or arterial thrombosis and/or foetal losses associated with characteristic laboratory abnormalities, such as persistently elevated levels of antibodies directed against membrane anionic phospholipids (ie, anticardiolipin [aCL] antibody, antiphosphatidylserine) or their associated plasma proteins, predominantly beta-2 glycoprotein I (apolipoprotein H), or evidence of a circulating anticoagulant.

In pregnancy, the placenta can be affected by small clots, and there is an increased risk of miscarriage, particularly in mid-pregnancy.

When only the symptoms of the antiphospholipid syndrome occur, this is known as primary antiphospholipid syndrome.

The secondary form occurs in association with another autoimmune disease, usually systemic lupus erythematosus. It can take 10 years or more for those with primary antiphospholipid syndrome to develop other features of SLE, however the majority with Primary APS do not go on to develop lupus in later life. [27]

Drug induced lupus

Presents as arthralgia, myalgia, fever and serositis in middle aged women. It is very important to consider this in the older patient who may be taking a number of medications. With increased use of minocycline for acne, some younger females are being seen with this variant. Although rashes may occur in one-third of cases the classic malar rash is rare. The drugs most frequently associated with the syndrome are

hydralazine, procainamide, isoniazid, sulphasalazine and penicillamine. The recognition of drug induced lupus is important as it reverts within a few weeks of stopping the offending drug.

Primary Sjögren's syndrome

Confusion with SLE may arise particularly in young patients where extraglandular features are marked, including peripheral polyarthritis, serositis and haematological complications such as neutropenia and lymphopenia. Sjögren's syndrome can often be distinguished by the recurrent parotid swelling, dry eyes and dry mouth and a vasculopathy of the lower legs which is peculiar to the disease. The high levels of gammaglobulin found in Sjögren's syndrome are thought to be the cause of the rash known as Walddenström's hypergammaglobulinaemic purpura.

Mixed Connective Tissue Disease

Mixed connective-tissue disease (MCTD) was first recognized in1972 among a group of patients with overlapping clinical features of systemic lupus erythematosus (SLE), scleroderma, and myositis, with the presence of a distinctive antibody against what now is known to be U1-ribonucleoprotein (RNP).

MCTD has been more completely characterized in recent years and is now recognised to consist of the following core clinical and laboratory features: Raynaud's phenomenon, swollen hands, arthritis/arthralgia, acrosclerosis, oesophageal dysmotility, myositis, pulmonary hypertension, high level of anti–U1-RNP antibodies, and antibodies against U1-70 kd small nuclear ribonucleoprotein (snRNP).

6. Treatment

SLE may be classified as mild (e.g, fever, arthritis, pleurisy, pericarditis, headache, rash) or severe (e.g, hemolytic anemia, thrombocytopenic purpura, massive pleural and pericardial involvement, significant renal damage, acute vasculitis of the extremities or GI tract or florid CNS involvement).

Mild or remittent disease:
Little or no therapy may be needed. Arthralgias are usually controlled with NSAIDs.
Antimalarials help, particularly when joint and skin manifestations are prominent. Hydroxychloroquine 200 mg once or twice daily reduces the frequency of SLE flares.
Alternatives include chloroquine 250 mg daily and quinacrine 50 to 100 mg daily. Hydroxychloroquine can rarely cause retinal toxicity so the eyes should be examined annually.

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Severe disease:
Corticosteroids are first-line therapy. A combination of prednisolone and immunosuppressants is recommended in active, serious CNS lupus, vasculitis especially that affecting viscera or nerves, or active lupus nephritis.
Prednisolone is usually given in doses of 40 to 60 mg daily, but the dose may vary according to the manifestation of SLE.
Oral azathioprine 1 to 2.5 mg/kg once/day or oral cyclophosphamide 1 to 4 mg/kg once/day can be used as an immunosuppressant.
For renal involvement, cyclophosphamide is usually given in intermittent IV "pulses" instead of daily oral doses; e.g, about 500 mg to 1 g/m^2 IV (together with mesna and fluid loading to protect the bladder) monthly for 6 months and then once every 3 months for 18 months (less frequently if there is renal or hematologic toxicity).

Improvement of severe SLE often takes 4 to 12 weeks. Thrombosis or embolism of cerebral, pulmonary, or placental vessels requires short-term treatment with heparin and longer treatment with warfarin, if the diagnosis of antiphospholipid syndrome is confirmed. The target INR is usually 3.

Suppressive therapy:
For most patients, the risk of flares can be decreased without prolonged high-dose corticosteroids. Chronic disease should be treated with the lowest dose of corticosteroids and other drugs that control inflammation (e.g, antimalarials, low-dose immunosuppressants).
Treatment should be guided by clinical features primarily, although anti–double-stranded DNA antibody titres or serum complement levels may be followed, and other pertinent blood and urine tests to assess specific organ involvement. Anti–double-stranded DNA antibody titres or serum complement levels may not parallel non-renal disease flares.

If a patient needs long-term high-dose corticosteroids, alternative oral immunosuppressants should be considered. Calcium, vitamin D, and bisphosphonate therapy should be considered in patients on chronic corticosteroids. [1]

Newer treatments

Although steroids have been the mainstay of treatment for decades, newer drugs have been developed, targeting the B-lymphocyte. B cell dysfunction is thought to play a central role in the pathogenesis of SLE, and various drugs targeting surface proteins are in development.

Rituximab is one of the most promising of these. It is a genetically engineered monoclonal antibody against the CD-20 surface antigen, and already has US FDA approval for use in non-Hodgkins lymphoma and RA resistant to TNFα inhibitors so much is already known about its safety profile. Rituximab reduces the level of CD-20^+ B cells in the blood. Early phase I and II trials have showed encouraging clinical results. Phase III trials are currently underway. [28]

Epratuzumab, aimed at CD-22^+ B cells, abatacept, and belimumab are other new drugs undergoing clinical trials, aimed at depleting dysfunctional B cells. There are potential side-effects, such as infection, although often this is seen in patients taking other immunosuppressive drugs as well so the exact role of the newer drugs is yet unclear. [29]

7. Prognosis and Main Disabling Effects

The course is usually chronic, relapsing, and unpredictable. Long term remission lasting for years is now possible with maintenance therapy.
If the initial acute phase is controlled, even if very severe (e.g, with cerebral thrombosis or severe nephritis), the long-term prognosis is usually good.

The prognosis in SLE has improved dramatically in the last 40 years.
The 10-year survival rate has risen from less that 50% in 1955 to over 90% in recent years in most developed countries. This is attributable to the use of steroid therapy, earlier recognition and general advances in the quality of medical care, including renal dialysis and better intensive care.

Provided the initial acute phase is controlled, the long term prognosis is good.
More severe disease requires more toxic therapies, which increase risk of mortality. Examples of such complications include infection from immunosuppression or osteoporosis from chronic corticosteroids. Osteoporosis is a recognised side-effect of long term steroid treatment but can be monitored with bone densitometry and calcium supplementation has a protective effect on this.

There is also an increased risk of cancer, particularly haematological disease. The causal mechanism is yet unknown and may be related to increased use of immunosuppressants in this patient population. [30]

Deaths related to active lupus, renal failure and infection tend to occur early in the disease, whereas deaths due to cardiovascular causes occur late.

Flare-ups can be triggered by sun exposure, infection, surgery, or pregnancy and occur less often after menopause.
The flares are readily and completely responsive to treatment and diminish in frequency and intensity over time [31].

Involvement of major organ systems may occur in the heart, lungs, kidneys or central nervous system. These are responsible for most of the mortality and morbidity including a chronic, progressive loss of organ function.
Fortunately most forms of major organ involvement in SLE are rare, with the notable exception of neurologic and renal disease.

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