Current Practice

Paediatric Lupus

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Introduction

Systemic lupus erythematosus (SLE) is a systemic disease with autoimmune aberration[1]. Almost every organ can be affected and no organ is spared[1]. Sixty five percent of patients with SLE have disease onset between the ages of 16 and 55 years[2]. In about 20%, the onset of the disease is before 16 years[2]. The clinical and immunological patterns of SLE in childhood-onset patients are slightly different from the disease in other patients[2]. Children are more likely to have severe organ involvement, especially nephritis, at the initial presentation[2]. Other major manifestations such as neurologic involvement, thrombocytopenia and haemolytic anaemia are also common initial features in the childhood-onset group[2]. Serologically, anti-double stranded DNA, anti-Sm, anti-RNP antibodies and low complement (C3) are all found more frequently in younger patients. Younger patients also require higher doses of steroids than adults. However, during the disease evolution process, the pattern is quite similar in childhood-onset and adult patients[2]. In the management of children, issues related to growth, both physical and psychosocial, are quite important.

Aetiology

There is a genetic predisposition in SLE[3]. In rare cases SLE may be associated with a deficiency of a single gene (e.g. the complement components of C1q and C4) but more commonly, it is due to the combined effect of variants of a large number of genes[3]. A recent large scale replication study identified risk loci for SLE[4]. Although these findings are promising, the loci identified so far can account for only 15% of heritability in SLE[5].

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When genetic predisposition is present, other factors, either endogenous or environmental, play a role in triggering of the disease. Environmental factors include ultraviolet (UV) light, medication and viruses, particularly EB viruses[6,7]. Endogenous factors include epigenetic, hormonal and the presence of an X chromosome[6,8].

Pathogenesis

When there is apoptosis, either induced by virus or virus like particles or UV light, released nucleic acids are taken by dendritic cells and converted to plasmacytoid dendritic cells. These plasmacytoid dendritic cells secrete interferon alpha on viral infection because of the activation of Toll like receptors 7 and nine[9]. Interferon alpha inducible genes are up-regulated in patients with SLE and interferon alpha is involved in all pathways of pathogenesis of SLE[10]. B cells and T cells are activated and produce auto antibodies. Then immune complex formation occurs and subsequent inflammatory reactions result in tissue damage[2].

Diagnosis

Diverse clinical manifestations of SLE present a challenge to the clinician. The American College of Rheumatology (ACR) classification criteria were formulated in 1971 and updated in 1997[2]. These criteria can be used in diagnosis. There is excellent sensitivity and specificity in established disease but not for early disease as SLE is a disease where organs are involved one after another. In 2012 SLICC criteria were introduced by the Systemic Lupus International Collaborating Clinics (SLICC) Group[11] (Table 1).

Table 1: ***Systemic Lupus International Collaborating Clinics (SLICC) criteria***[11]

Requirement: ≥ 4 criteria (at least one clinical and one laboratory criterion OR biopsy proven lupus nephritis with positive ANA or anti-ds DNA)

Clinical Criteria

1. Acute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral or nasal ulcers
4. Non-scarring alopecia
5. Arthritis
6. Serositis
7. Renal
8. Neurologic
9. Haemolytic anaemia
10. Leukopenia
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-ds DNA
3. Anti-Sm
4. Antiphospholipid Ab
5. Low complement (C3, C4, CH 50)
6. Direct Coombs' test (do not count in the presence of haemolytic anaemia)

Serology in SLE

Even though the presence of auto antibodies in SLE has been known for more than 60 years, even now, a great effort is made to understand pathogenetic, diagnostic and prognostic value of such antibodies[12]. Table 2 illustrates the diagnostic utility of ANA, Anti-dsDNA, Anti-Sm, Anti-histone, Anti-Ro and Anti-La antibodies. Another important group of antibodies is antiphospholipid antibodies[12]. Anti-ribosomal P antibodies are also specific to SLE and there is an association with neuropsychiatric lupus[12]. Anti-C1q is useful to monitor evolution of lupus nephritis.

Table 2: ***Correlation between antibodies in SLE and diagnostic utility***[12]

Antibody	Diagnostic utility	Associated lupus subtypes	Other associated diseases
ANA	High sensitivity Low specificity	SLE (98%), LN (100%), Drug induced lupus, Discoid lupus (35%), MCTD	JIA, DM, RA, Malignancies, Chronic infections, Relapsing polychondritis, Thyroid disease, SS, SSc, Hepatic disease
Anti-dsDNA	High sensitivity & specificity for SLE Correlates with disease activity	SLE (70-98%), LN (70%), Neuropsychiatric lupus (44-82%)	HIV, parvovirus B 19 infection, myeloma, type 1 autoimmune hepatitis
Anti-Sm	Low sensitivity High specificity	SLE (20-40%), LN (14%), MCTD (8%)	EBV infections
Anti-histone	Low Ig M High IgG	SLE (70%), LN (37%), Drug induced SLE (96-100%)	RA ,SSc, PBC, dementia, infections
Anti-SSA/Ro	High prognostic	SLE (30%), LN (31%), NLE especially congenital heart block (90%), SCLE (70-80%), Discoid lupus (5-20%)	SSc, PBC, RA, SS
Anti-SSB/La	Moderate	SLE (30%), LN (14%), SCLE (30%), NLE (90%)	SS

SLE: Systemic lupus erythematosus, LN: Lupus nephritis, MCTD: Mixed connective tissue disease, JIA: Juvenile idiopathic arthritis, DM: Diabetes mellitus, RA: Rheumatoid arthritis, SS: Sjogren syndrome, SSc: Systemic sclerosis, HIV: Human immunodeficiency virus, EBV: Epstein-Barr virus, PBC: Primary biliary disease, NLE: Neonatal lupus erythematosus, SCLE: Subacute cutaneous lupus erythematosus

Neonatal lupus erythematosus (NLE)

This is a passively transferred autoimmune disease that occurs in some babies born to mothers with anti-SSA/Ro and/or anti-SSB/La antibodies[2]. The most serious complication in the neonate is complete heart block, which occurs in up to 2% of such pregnancies[2]. Isolated skin rash occurs in a similar percentage[2]. Once a mother has given birth to an infant with congenital heart block the recurrence rate is about 15%[2].

Monitoring of the disease

Assessment of activity in a patient with SLE is crucial as it forms the basis for most treatment decisions. There are several validated activity indices which can be used in research as well as clinical practice. As SLE can manifest in many different guises, a thorough history and physical examination including all major systems, must be undertaken at each visit. Any new symptoms/signs or changes in symptoms/signs since the patient's previous visit require further evaluation. The blood pressure and urine analysis must be checked at each clinic visit.

Laboratory assessment can be used to assess disease activity and organ damage. Full blood count, erythrocyte sedimentation rate, C-reactive protein, liver function tests, urine analysis and serum creatinine should be checked at each visit[13]. Rapidly rising levels of serum creatinine imply that renal activity is "turning into damage". Urine analysis for red and white cells, proteins and cellular casts are useful tests of renal activity and may reveal clinically silent renal disease. If these tests are abnormal, further investigations including protein/creatinine ratio estimation should be undertaken together with renal ultrasound imaging. Renal biopsies are recommended in those with persistently abnormal urine analysis or a reduced glomerular filtration rate.

Antibodies to dsDNA may fluctuate with disease activity in many patients but not in all. Rising antibodies to dsDNA should alert the clinician that a flare-up is imminent and should call for increased surveillance, particularly when associated with falling levels of C3 and C4. Other routinely available antibodies have not been demonstrated to be helpful as a marker of lupus activity.

Treatment options

In the management of SLE, antimalarial drugs, glucocorticoids and immunosuppressive drugs including cyclophosphamide, azathioprine, methotrexate and mycophenolate mofetil (MMF) are used[1]. The choice of the drug is determined largely by the severity of the disease and function of the involved organ[1]. The antimalarial agent hydroxychloroquine has therapeutic value and limited toxicity. It inhibits the function of toll like receptors that contribute to autoimmunity[14]. Antimalarial drugs reduce organ damage over time, reduce disease flares and in patients with renal disease on immunosuppressives there is better outcome in a group given hydroxychloroquine than in controls[14]. Therefore, it is indicated in all patients with SLE even during remission.

Renal Disease

In proliferative glomerulonephritis the efficacy of intravenously administered cyclophosphamide is established[15]. Induction dosing regimen is comparable between low dose two weekly versus high dose monthly for 6 months. MMF is a reversible inhibitor of inosine monophosphate dehydrogenase, an enzyme involved in purine synthesis of activated T cell proliferation[16]. In a recent open labelled randomized controlled international study, no difference in efficacy or safety in comparison to intravenous cyclophosphamide was noted although non-Caucasians /Asians responded more to MMF and MMF and azathioprine were seen to have the same efficacy in maintenance of remission[16]. B cell depletion therapies include Rituximab which is a chimeric monoclonal antibody against CD 20[17]. Open label, uncontrolled studies and case series suggest favourable outcome in a range of refractory disease nephritis, central nervous system disease, vasculitis and thrombocytopenia[17]. A trial of rituximab in patients with moderate to severe SLE failed to reach primary end points[17]. Thus the role of B cell depletion in the treatment of SLE is unclear. Belimumab is a human monoclonal antibody against B lymphocyte stimulator (BlyS)[18]. BlyS is a cytokine that is involved in the survival of B cells, germinal centre formation and T cell dependent immunoglobulin class switching[1]. Belimumab resulted in small but significant beneficial clinical effect within the first year of treatment with mild to moderate disease[18].

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