Meet the Expert

Management of CNS and Kidney Involvement in SLE

12th January, 2008

Hall G

17.00 to 18.30 hrs.

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Our modern awareness of SLE dates to the 1930’s. SLE is the most common of the connective tissue disease that is characterized by ANA positivity and immune mediated tissue damage with female preponderance & M:F ratio of 1:13. The organ damage is due to loss of immune tolerance to self antigens directed against nucleic acids and other intracellular proteins. SLE is a multisystem disorder with protean manifestations that evolve over years. The clinical spectrum of SLE is wide and ranges from benign easily treated disease with rash, arthritis, fatigue, to a very severe life threatening illness with progressive nephritis leading to renal failure or irreversible CNS damage. SLE is characterized by flares of rampant inflammation that can threaten, in an unpredictable, manner, almost any organ in the body, including the brain, kidney and heart.

**Age:** Most patients develop nephritis early in their disease and it is uncommon to have the original onset of renal disease more than ten years after the appearance of SLE. SLE is more common among women in the third decade of life and lupus nephritis occurs in patients aged 20-40 years.

**Race:** SLE is more common in black people and Hispanic people than in white people. Black people and Asian people may have a higher prevalence of more severe lupus nephritis than other ethnic groups.

**SLE- Immune abnormalities**

The immune abnormalities in SLE give rise to production of pathogenic antibodies. Impaired T-and B- lymphocyte regulation leads to defective clearance of autoantigens and immune complexes. The majority of autobody found in SLE are targeted at intracellular nucleoprotein particles. 98% of patients possess antinuclear antibodies and Anti- dsDNA antibodies are found in 50-80% of patients. T cell dysfunction in SLE leads to skewed cytokine production, particularly deficient production of Il-1. Defective T cell regulation of B cell immunoglobulinemia gives rise to inappropriate production of multiple autoantibodies, formation and deposition of immune complexes in tissues, inflammation and organ failure.

**Antibodies in SLE**

Since SLE is associated with a number of autoantibodies, it is important to understand their relevance in clinical practice. Some of these are useful as diagnostic markers, others help in quantifying disease activity and still others are primarily of research interest, making no contribution to patient care.

**Antinuclear antibody (ANA)**

ANA is a good screening test for SLE because 95%of cases show a high titre (1:80 or more) of this autoantibody. Thus, the specificity of ANA for diagnosis of SLE is quite low (app. 40% only). The gold standard method for testing and reporting ANA is the indirect immunofluorescence method. Different types of staining patterns can be identified by this method such as homogeneous (diffuse), speckled (fine, coarse), rim (peripheral) and nucleolar. Also, performing serial titres of ANA in a diagnosed case of SLE is of no clinical value because it does not correlate well with disease activity.
Anti-double stranded DNA antibody (anti-dsDNA)

This test has high specificity for SLE. Farr assay (radioimmunoassay) and Crithidia lucilae method are very good in this regard but they are cumbersome and hence not very popular with most laboratories. Newer methods such as ELISA and haemagglutination have become available and are reasonable alternatives. The positivity of anti-dsDNA in SLE at the time of presentation is in the range of 60% (although the cumulative positivity during the course of disease may approach 90%). The anti-dsDNA titres most often correlate with disease activity.

SLE is a relapsing disease. Relapses are not only a burden to the patient but are also frequently associated with the occurrence of irreversible damage, either due to the disease or its treatment. Anti ds-DNA reflects the disease process and serial measurement of these antibody may allow the early detection of upcoming disease activity. Using this approach Swaak et al observed a pattern in which a sharp drop in anti-dsDNA levels occurred at the time of a relapse. Concomitantly, a decrease in complement levels occurred, particularly during a renal relapse. Interestingly, anti-dsDNA levels rose prior to the relapse. A comparable pattern, that is, increase of anti-dsDNA prior to relapse and decrease at the time of flare is observed. It is hypothesized that the decrease in anti-dsDNA is due to deposition of anti-dsDNA in renal tissue at the time of relapse.

Antibodies to extractable nuclear antigens (anti-ENA)

These include anti-Sm, anti-U1RNP, anti-Ro and anti-La antibodies. High titres of anti-U1RNP are associated with mixed connective tissue disease (MCTD) which is a subset of SLE with prominent Raynaud’s phenomenon, sclerodactyly, proximal myopathy and mild or no renal involvement. Anti-Sm antibody is quite specific for SLE but it is found only in 10-30% of patients. It is indicated in a patient who is ANA negative but satisfies SLE features. Anti-Ro is associated with congenital heart block, neonatal SLE anti-La is associated with SLE and Sjogren’s syndrome. Antihistone antibodies are associated with drug induced SLE.

Complement levels (C3 and C4): These two complement components are useful in the diagnosis and follow up of SLE. Their levels drop because of consumption. C3 and C4 levels are negatively correlated with lupus activity.

ACR criteria

These classification criteria were devised for classifying SLE patients for inclusion in clinical or laboratory research studies. These are not diagnostic criteria (though they serve the purpose). These criteria emphasize the multi-system nature of the disease and the diagnosis requires much more than a positive ANA alone. 4 criteria are required for study purposes. However a clinical diagnosis of lupus may be bestowed in the absence of four criteria.

A person shall be said to have SLE if four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Clinical features of SLE

Skin rashes- Acute inflammatory rashes occur over the major regions of the face predominantly malar area and in between the interphalangeal joints of the fingers and on sun exposed areas of trunk or upper extremity. Chronic discoid scarring rashes occur on the face, scalp, ears and upper extremity.

Arthritis- Most common pattern of arthritis is symmetrical polyarthritis that mimicks RA and a migratory oligoarthritis. 10% of SLE patients develop deforming type of arthritis of hands.
Management of CNS and Kidney Involvement in SLE

**Haematologic Disorder:** Haematologic manifestations include anaemia, leucopenia and thrombocytopenia. DVT, stroke, TIA, recurrent pregnancy loss, livido reticularis are characteristic features of APLA syndrome.

**Lupus Nephritis**

Lupus nephritis is an inflammation of the kidney that usually arises within 5 years of SLE diagnosis. Histological evidence of lupus nephritis is present in most patients with SLE, even if they do not have clinical manifestations of renal disease. The symptoms are generally related to hypertension, proteinuria, and renal failure. Renal involvement in systemic lupus erythematosus is a strong predictor of poor outcome. The prevalence of renal disease varies from 31 to 65%. The general consensus is that 50% lupus patients will develop clinically relevant nephritis at some time in the course of their illness.
High risk features of Lupus nephritis

Cellular crescents and interstitial fibrosis have emerged as the most predictive active pathological feature and chronic histological prognostic factor respectively. Combination of these morphological attributes, identifies particularly high-risk individuals. Patients with 50% or more cellular crescents and those with less extensive cellular crescents plus moderate to severe interstitial fibrosis are at markedly increased risk for doubling serum creatinine compared to those who lack these histologic features \( (P < 0.0001) \). Azotaemia, anaemia, hypo-complementaemia, hypertension, tubular atrophy and glomerular sclerosis are also associated with an increased probability of renal function deterioration. Serum creatinine, haematocrit, race, and kidney pathology data together work as independent predictors of renal insufficiency.

Clinical features

Patients with active lupus nephritis often have either symptoms of active systemic lupus erythematosus (SLE), including fatigue, fever, rash, arthritis, serositis or CNS disease. These are more common with focal proliferative and diffuse proliferative lupus nephritis. Nephritis is characterised by peripheral edema secondary to hypertension or hypoalbuminemia. Extreme peripheral edema is more common in persons with diffuse proliferative or membranous lupus nephritis as these renal lesions are commonly associated with heavy proteinuria. Headache, dizziness, visual disturbances, and signs of cardiac decompensation are commonly related to hypertension.

Laboratory Diagnosis

Laboratory tests to evaluate renal function include:

- Blood urea nitrogen
- Serum creatinine level
- Urinalysis (for protein, RBCs, and cellular casts)
- Twenty-four–hour urine test for creatinine clearance
- Twenty-four–hour urine test for protein excretion

Tests of SLE Renal disease activity

Disease activity can be evaluated with:

- Anti-dsDNA titres
- Anti-nucleosome antibodies
- Complement determinations \( (C3, C4, \text{ and } CH_{50}) \),
- ESR

ESR is generally elevated and anti-dsDNA and C3, C4 levels are reduced especially with focal proliferative and diffuse proliferative lupus nephritis.

1. Clinically relevant lupus nephritis is associated with a 30% decrease in creatinine clearance, proteinuria of greater than 1000 mg/d, and renal biopsy findings indicating active lupus nephritis.

2. Anti-nucleosome antibodies appear early in the course of the autoimmune response in SLE. They have high sensitivity and specificity for the diagnosis of SLE, and the titers correlate with disease activity.
3. Anti-C1q antibodies are associated with lupus nephritis; higher titers correlate with active renal disease.

Table No. 2 gives description and scores to assess SLE disease activity at bed side.

**Table 2- SLE disease activity (SLEDAI)**

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>Recent onset, exclude metabolic, infectious or drug causes</td>
<td>8</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, markedly loose associations, impoverished thought content, markedly illogical thinking, bizarre, disorganised or catatonic behaviour. Exclude uraemia and drug causes.</td>
<td>8</td>
</tr>
<tr>
<td>‘Organic brain syndrome’ or Acute confusional state</td>
<td>Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, drug or infectious cause</td>
<td>8</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>Retinal changes of SLE. Include cytoid bodies, retinal haemorrhages, serous exudates/haemorrhages in choroid or optic neuritis. Exclude hypertension, infection or drug cause</td>
<td>8</td>
</tr>
<tr>
<td>Cranial nerve disorder</td>
<td>New onset of sensory or motor neuropathy involving cranial nerves</td>
<td>8</td>
</tr>
<tr>
<td>Lupus headache</td>
<td>Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.</td>
<td>8</td>
</tr>
<tr>
<td>CVA</td>
<td>New onset of CVA. Exclude atherosclerosis</td>
<td>8</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Ulceration gangrene, tender finger nodules, periungual infarction, splinter haemorrhages, or biopsy or angiogram evidence of vasculitis</td>
<td>8</td>
</tr>
<tr>
<td>Arthritis</td>
<td>≥ 2 joints with pain and signs of inflammation (tenderness, swelling or effusion)</td>
<td>4</td>
</tr>
<tr>
<td>Myositis</td>
<td>Proximal muscle aching/weakness, associated with elevated CPK/aldolase or EMG changes or biopsy evidence of myositis</td>
<td>4</td>
</tr>
<tr>
<td>Urinary casts</td>
<td>Haemoglobin, granular or RBC casts</td>
<td>4</td>
</tr>
<tr>
<td>Haematuria</td>
<td>&gt; 5 RBC/HPF. Exclude stone, infection or other cause</td>
<td>4</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>&gt; 0.5 grams/24 hrs.</td>
<td>4</td>
</tr>
<tr>
<td>Pyuria</td>
<td>&gt; 5 WBCs/HPF. Exclude infection</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>Inflammatory type rash</td>
<td>2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Abnormal, patchy or diffuse loss of hair</td>
<td>2</td>
</tr>
<tr>
<td>Mucosal ulcers</td>
<td>Oral or nasal ulcerations</td>
<td>2</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>Pleuritic chest pain with pleural rub/effusion/pleural thickening</td>
<td>2</td>
</tr>
<tr>
<td>Low complement</td>
<td>Decrease in CH50, C3 or C4 below the normal limit of Lab</td>
<td>2</td>
</tr>
<tr>
<td>Increased DNA binding</td>
<td>Increased DNA binding using Farr assay</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>&gt; 38 Deg C. Exclude infection</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>&lt; 100,000/cu mm, exclude drug cause</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>&lt; 3000/cu mm, exclude drug causes</td>
<td>1</td>
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**SLEDAI Outcomes**

Score is helpful for prognosticating the patient outcome and planning therapy.

SLE: Flare - An increase in SLEDAI > 3;

Improvement - A reduction in SLEDAI of > 3;
Persistently active disease - Change in SLEDAI +/- 3;

Remission  SLEDAI of 0.

These outcomes will allow a more complete description of patient’s response to therapeutic intervention in a responder index.

A number of other validated indices are available for quantifying disease activity. The more popular indices include-BILAG17, SLEDAI18, SLAM19 and LAI.20 these help in formulating the overall treatment plan and assessment of prognosis.

**Renal biopsy**

- Renal biopsy should be considered for any patient with SLE who has clinical or laboratory evidence of active nephritis (active urinary sediments, RBCs albuminuria with 24 hr urinary protein >500mg) especially with the first episode of nephritis.
- Renal biopsy may be useful in patients with recurrent episodes of nephritis, by revealing the histologic pattern and stage of disease (activity and chronicity). Renal biopsy is useful in determining prognosis and planning treatment.
- If a particular patient has other manifestations of SLE (eg, severe CNS or hematologic involvement) and will be treated with cyclophosphamide, a biopsy may not be necessary but should still be considered because it may help predict renal outcome.

**Staging**

- Pathologic classification

  The classification of lupus nephritis was revised by the International Society of Pathology/Renal Pathology Society (ISN/RPS) in 2003 and is based on light microscopy, immunofluorescence, and electron microscopy findings from renal biopsy specimens. (Refer table 3). In addition to the pathologic classification, activity and chronicity indices are scored pathologically and predict the renal prognosis (progression of renal disease) The activity index reflects the state of active inflammation observed at biopsy, which may be reversible with medical therapy. The chronicity index reflects the amount of fibrosis and scarring, which are unlikely to respond to therapy. Renal lesions with a high activity index are more likely to respond to aggressive therapy, whereas renal lesions with high chronicity are not.

**ACLA and Renal Lupus**

14-53% patients of SLE are ACLA positive. ACLA is a pathogenic antibody predisposing to thrombosis. The renal manifestations are protienuria and hypertension.

  The renal histological markers are:

1. Glomerular sclerosis
2. Tubular atrophy
3. Interstitial fibrosis

  All these add to the chronicity index of SLE renal disease and form the prognostic indicators of renal outcome. Looking at the benefits of anticoagulation and thromboprophylaxis, it is mandatory to prescribe life long above agents to lupus patients with positive ACLA.

**Treatment of SLE and Nephritis**

The biological behaviour of the lupus nephritis with remitting and relapsing course and evolution from WHO class II to class IV indicates appropriate use of steroids and immunosuppression after kidney biopsy. Effective treatment in lupus nephritis depends on
the recognition of early phase of renal involvement, prior to scaring, atrophy and fibrosis. SLE is a chronic disease with periods of remission and relapses, it is unclear whether relapses should be treated in the same fashion as the initial presentation.

**Patient education**

A knowledgeable patient who understands the disease is more likely to be compliant with appointments and medication. Establishing a good doctor–patient relationship is fundamental to the management of any chronic disease. It is often useful to offer a new patient the opportunity to interact with other previously diagnosed lupus patients who are identified by the specialist as having a positive outlook of the disease and the enthusiasm to function as counsellors. In many advanced centres (outside India), community-based lupus support groups exist and they perform this vital function. The need for long-term treatment and careful monitoring of various parameters must be emphasized.

**General measures**

It is advisable to restrict salt if hypertension is present, fat if hyperlipidemia or nephritic syndrome is present, protein should be restricted if azotaemia is present and calcium should be supplemented with steroid therapy consider bisphosphonates. Meticulous control of hypertension is desirable. Pregnancy should be avoided during active lupus nephritis with suitable contraception. NSAIDs should be avoided in the presence of impaired renal function.

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**Table 3 : International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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</table>
| I     | Minimal mesangial lupus nephritis  
Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence |
| II    | Mesangial proliferative lupus nephritis  
Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy. |
| III   | Focal lupus nephritis*  
Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations |
| IV    | Diffuse lupus nephritis*  
Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation. |
| V     | Membranous lupus nephritis  
Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations. Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed. Class V lupus nephritis may show advanced sclerosis |
| VI    | Advanced sclerotic lupus nephritis  
≥90% of glomeruli globally sclerosed without residual activity |
Antimalarials

These drugs are particularly useful for cutaneous manifestations of SLE. These agents have multiple properties: immunosuppressive anti-inflammatory and sun-blocking. They are also reported to possess anti-platelet and cholesterol lowering effects. The drug of choice is hydroxychloroquine (200 mg BD for 3 months and then 200 mg daily). The maintenance dose must not exceed 6 mg/kg/day. Although the incidence of retinal toxicity is very low, annual monitoring of vision with perimetry using a red object is recommended (for chloroquine, 6-monthly monitoring is desirable). The drug must be discontinued if a central scotoma is detected at any stage. Other significant side effects include nausea, pruritus, hyperpigmentation, myopathy and rarely psychosis. Use of hydroxychloroquine during pregnancy is controversial. When antimalarials are withdrawn after prolonged administration, some patients may develop a relapse of lupus activity. In refractory cases, quinacrine may be combined with hydroxychloroquine. Alternatives include dapsone and thalidomide.

Therapies for specific types of lupus nephritis based on renal pathology

Class I: Minimal mesangial lupus nephritis requires no specific therapy.

Class II: Mesangial proliferative lupus nephritis may require treatment if proteinuria is greater than 1000 mg/d. Consider prednisone in low- to- moderate doses (ie, 20-40 mg/d) for 1-3 months, with subsequent taper.

Classes III and IV: Patients with either focal or diffuse lupus nephritis are at high risk of progressing to end-stage renal disease and require aggressive therapy. Administer prednisone 1 mg/kg/d for at least 4 weeks, depending on clinical response. Then, taper it gradually to a daily maintenance dose of 5-10 mg/d for approximately 2 years. In acutely ill patients, intravenous methylprednisolone pulses of up to 1000 mg/d for 3 days may be used to initiate corticosteroid therapy.

Use immunosuppressive drugs in addition to corticosteroids in patients who do not respond to corticosteroids alone, who have unacceptable toxicity to corticosteroids, who have worsening renal function, who have severe proliferative lesions, or who have evidence of sclerosis on renal biopsy specimens. Both cyclophosphamide and azathioprine are effective for proliferative lupus nephritis, although cyclophosphamide is apparently more effective in preventing progression to end-stage renal disease. The standard induction regimen which traditionally associates cyclophosphamide (CYC) with corticosteroids still remains the best option to preserve renal function in patients with proliferative lupus nephritis. Solid evidence shows that this drug combination administered either traditionally (corticosteroid and monthly _IV CYC as used in US studies) or in modified regimen (smaller doses of CYC given at weekly or fortnightly interval over a shortened treatment duration, more frequently used in Europe) can induce a complete or partial remission in more than 80% of patients with proliferative lupus nephritis. Consequently 10- year survival rates now surpass 75% and continue to improve. CYC, given either orally or as intermittent pulses together with corticosteroid has been demonstrated by randomized controlled National Institute of Health (NIH) trials Mycophenolate mofetil has been shown to be effective in treating these patients and may be used alone or sequentially after a 6-month course of intravenous cyclophosphamide.

Class V: Patients with membranous lupus nephritis are generally treated with prednisone for 1-3 months, followed by tapering for 1-2 years if a response occurs. If no response occurs, the drug is discontinued. Immunosuppressive drugs are generally not used unless renal function worsens or a proliferative component is present on renal biopsy samples. Some clinical evidence indicates that azathioprine, cyclophosphamide, cyclosporine and
chlorambucil are effective in reducing protienuria. Mycophenolate mofetil may also be effective.

Rituximab, a B-lymphocyte-depleting therapy, appears to be effective in SLE and is being investigated as a treatment for SLE and lupus nephritis. B cell depletion therapy with Rituximab is an efficacious and safe treatment for ITP and AIHA in pediatric SLE. Infliximab, a tumour necrosis factor (TNF)-alpha antagonist, was beneficial in a small series of patients with SLE, including in a large controlled trial in preventing flares of lupus nephritis, although it did reduce levels of anti ds-DNA antibodies.

**End- stage renal disease**

Patients with end-stage renal disease need dialysis and are good candidates for kidney transplantation. Patients with end-stage renal disease secondary to SLE represent 1.5% of all patients on dialysis in the United States. The survival rate among patients on dialysis is fair (ie, 5-y survival rate of 60-70%) and is comparable with patients on dialysis who do not have SLE.

Hemodialysis is preferred over peritoneal dialysis because several studies have documented higher anti-dsDNA levels, more thrombocytopenia, and higher steroid requirements in patients with SLE and end-stage renal disease who are on peritoneal dialysis. Hemodialysis also has anti-inflammatory effects with decreased T-helper lymphocyte levels. SLE is generally quiescent in patients on hemodialysis, although flares, including rash, arthritis, serositis, fever and leukopenia may occur and require specific treatment.

**Supportive therapy**

- **Antiplatelet**: Aspirin (150 mg) day is given on a long term to prevent thrombosis in those with DVT, CVA and APLA positive status.

- **Anticoagulants**: anticoagulant are indicated in patients with thrombosis of arterial and venous circulation and recurrunt fetal loss due to ACLA.

- **Antihypertensive**: The hypertension in SLE is high renin hypertension. Besides vasodilators (CCB) use of tissue specific ACE inhibitors (Quinalapril), is beneficial on long term due to their vasodilatory, protienuria stabilizing properties. BP should be brought down to less than 130/80 mm Hg.

- **Statins**: These are indicated in patients with Nephrotic syndrome and patients who have developed steroid induced hyperlipidemia. Besides lipid stabilization they have anti-inflammatory properties. They are useful in reducing the incidence of inflammatory and steroid related atherosclerosis in SLE.

- **Bisphosphonates**: Patients with SLE develop osteoporosis due to chronic inflammation and steroid abuse. Introduction and long term usage of bisphosphonates prevents osteoporosis and reduces the incidence of future fractures.

- **Folic Acid, B6, B12**: This are recommended to prevent the onset of Hyperhomocysteinemia HHC and its consequences.

**Infection prevention protocol**: Given as long as daily prednisolone is upto 20 mg/day or patient is lymphopenic.

- Sulphamethoxazole + Trimethoprim D S, twice daily every alternate day for PCP and Toxoplasmosis.
- Isoniazid for prophylaxis against tuberculosis.
- Fluconazole 400mg/weekly for fungal infections.
Follow up care

After starting treatment patients need good follow up care to prevent relapse of disease and also to avoid adverse effects due to cytotoxic drugs.

- ESR, anti-dsDNA, and C3 and C4 are used to monitor SLE disease activity.
- After the initiation of cytotoxic therapy every 3 monthly determine renal function, urinalysis for active renal sediments, albumin/CREATinine clearance and 24- hour urinary protein excretion. As the patient’s condition stabilizes, monitoring may be less frequent.
- Cyclophosphamide therapy requires regular laboratory monitoring, of CBC platelet count and urinalysis for RBCs.
- Azathioprine and mycophenolate mofetil therapy requires regular monitoring of CBC platelet count and less frequent monitoring of liver function test results.
- Special care to be given during flares of lupus nephritis. Less serious flare requires stepping up of steroid dose for short period and serious flare requires more aggressive treatment.

Prognosis

- **Excellent prognosis**: Minimal mesangial lupus nephritis and mesangial proliferative lupus nephritis (ISN/RPS 2003 classes I and II) carry an excellent prognosis.
- **Good prognosis**: Focal lupus nephritis (ISN/RPS 2003 class III) carries a good prognosis, with only a minority of patients developing progressive renal failure.
- **Fair prognosis**: Diffuse lupus nephritis (ISN/ RPS 2003 class IV) carries a fair prognosis, with a significant number of patients developing progressive renal failure. Membranous lupus nephritis (ISN/RPS 2003 class V) carries a fair prognosis, with a significant number of patients developing progressive renal deterioration gradually over time.
- **Poor prognosis**: Advanced sclerosing lupus nephritis (ISN/RPS 2003 class VI) carries a poor prognosis.

KEM SLE Cohort-Total 251 patients (2006-07)

**SLE with Lupus Nephritis-98 (Biopsy proven)**

- WHO Cl II- 28
- WHO Cl III- 3
- WHO Cl IV- 56
- WHO Cl V- 11
- CNS lupus- 17
- SLE with ACLA -103
- Lupus Nephritis with ACLA- 63
- SLE with nephrotic syndrome- 34
- SLE with *infections* – 31(predominantly Herpes zoster and LRTI)

(Dr L.S. Bichile, Dr. Archana Sonawale, Dr. Deepali Sen, Dr. Vaibhav Chewoolkar, Dr. Ram Shekhar Menon)
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KEM Lupus Nephritis Study I- Monthly CYC for 6 months

Total patients 25 Age 10-60 yrs

<table>
<thead>
<tr>
<th>WHO class</th>
<th>II</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>7</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>High ds-DNA</td>
<td>2</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Asym. proteinuria</td>
<td>6</td>
<td>5</td>
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<td>Low C3</td>
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<td>Low C4</td>
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<td>AI+CI&gt;6</td>
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Study period 0-6 months

<table>
<thead>
<tr>
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<tr>
<td>Average C3 levels</td>
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<tr>
<td>3</td>
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<td>51</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>59</td>
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<tr>
<td>Average proteinuria levels (gm/day)</td>
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<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
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</tr>
<tr>
<td>6</td>
<td>0.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Conclusions study I

- WHO classification correlates with clinical, biochemical & immunological parameters
- All classes show improvement on therapy
- Activity and chronicity can predict response to therapy
- AI+CI >6-delay in response to therapy.
- Pulse CYC effective over 6 months in normalizing biochemical & immunological parameters.

KEM Lupus Nephritis Study II

Low dose bimonthly CYCs for 3 months and maintenance with azathioprine for 1 year

15 patients, 15 controls

<table>
<thead>
<tr>
<th>Months</th>
<th>Creat. Avg (mg)</th>
<th>Low C3 Cases/controls</th>
<th>Low C4 (%) Cases</th>
<th>Urine Albumin (gm/d)</th>
<th>SLEDAI sc (Avg)</th>
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<tbody>
<tr>
<td>0</td>
<td>1.12</td>
<td>14/14</td>
<td>70</td>
<td>2.3</td>
<td>22</td>
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<tr>
<td>3</td>
<td>0.96</td>
<td>6/13</td>
<td>24</td>
<td>0.76</td>
<td>8</td>
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<tr>
<td>6</td>
<td>0.92</td>
<td>2/10</td>
<td>18</td>
<td>0.69</td>
<td>6.8</td>
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<tr>
<td>12</td>
<td>0.89</td>
<td>4/6</td>
<td>24</td>
<td>0.64</td>
<td>6.2</td>
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**Lupus Nephritis WHO class**

Dr. L.S. Bichile, Dr. Ramshekhar Menon, Dr. Archana Sonawale, Dr. Vaibhav Chewoolkar, Dr. Pranesh Raj

**Conclusions study 2**

- Low dose CYC followed by Azathioprin-clinical results comparable to high dose
- Rapid fall in proteinuria in early months of therapy
- Early normalization of complement as compared to high dose.
- Rapid fall in SS score in early months
- Less incidence of infections
- Patients with high grade proteinuria had high incidence of ACLA positivity (~53%)

**KEM Study III- Lupus nephritis with ACLA positive- CYC monthly for 6mts and 3 monthly for 8 doses Two and half year study**

48 patients

<table>
<thead>
<tr>
<th>Urine albumin</th>
<th>Urine albumin at 1yr</th>
<th>Low complements</th>
<th>Low com at 1yr</th>
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<tbody>
<tr>
<td>ACLA</td>
<td>Pos</td>
<td>Neg</td>
<td>&gt;1g</td>
</tr>
<tr>
<td>Neg</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Pos</td>
<td>28</td>
<td>15</td>
<td>13</td>
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</table>

**WHO class v/s ACLA and APSN-Repeat biopsy at the end of 1 year**

<table>
<thead>
<tr>
<th>ACLA</th>
<th>IIb</th>
<th>IV</th>
<th>IVd/Vd</th>
<th>Vb</th>
<th>Vd</th>
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<tr>
<td>POSITIVE</td>
<td>14</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Negative</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
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</tbody>
</table>

**1 year APSN**

<table>
<thead>
<tr>
<th>ACLA</th>
<th>II b</th>
<th>IV</th>
<th>yes</th>
<th>no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>

Dr. L.S. Bichile, Dr. Ramshekhar Menon, Dr. Pranesh Raj, Dr. Archana Sonawale, Dr. Vaibhav Chewoolkar.

**Conclusion Study- III**

- Anticardiolipin antibody has a high association with lupus nephritis
Management of CNS and Kidney Involvement in SLE

• Although there is no difference in the level of azotemia, the response in terms of hypocomplementemia is slower in aCL positive patients; especially into 6 months of therapy. Proteinurin did not correlate as significantly with the trends of hypocomplementemia.

• aCL positivity contributes to greater incidence of interstitial fibrosis, tubular atrophy and capillary wall thickening in biopsy specimens. The acute lesions of APSN possibly do tend to resolve in response to therapy.

• Anticoagulation with warfarin and thromboprophylaxis with aspirin prevents thrombogenecity

• High level anticoagulation in patients with thrombotic manifestations is unquestionable.

C.N.S. Lupus

Potential CNS involvement has been recognized ever since the multisystem nature of the disease first was appreciated. Clinical features include neurological (N) and psychiatric (P), manifestations. Disease involves both the central and peripheral nervous systems. CNS involvements predominates over peripheral nervous system disease. CNS disease may take the form of a diffuse disease [Psychosis, Depression, Cognitive dysfunction] or focal disease (stroke or transverse myelitis).

Etiology N.P SLE

The neurologic manifestations in lupus are multifactorical. These could be explained on the basis of –

• SLE vaculopathy- vasculitis, thrombosis

• Antibody mediated process- Anti neuronal antibody
  Anti ribosomal P antibody
  Anti Phospholipids

• Local production of Inflammatory mediators – IL2,-6,8,&10
  Or secondary to disease complications such as hypertension, atherosclerosis, thrombosis or infection.

SLE vaculopathy

Neuropathologic studies have revealed a bland noninflammatory vaculopathy involving the small vessels. Inflammatory disease of the small or large vessels is rare.

Brain micro infarcts are associated with microangiopathy. MRI documents small vessel infarcts and serve as a surrogate for brain biopsy.

Auto antibodies

Specific immune response is directed against the autoantigens on neurons, ribosome and phospholipids associated proteins. There is a definite temporal relationship between clinical events and serologic findings, presence of auto antibodies in CSF and identification in neuronal tissue.

N.D.A (N-methyl- D aspartate) receptors NR2a and NR2b bind the neuro transmitter glutamate. These receptors are rich in forebrain and hippocampus and are closely related to learning and memory. Anti NR2 glutamate receptor antibodies have pathogenic role in NR2 subset of patients with cognitive decline or psychosis.
Antiphospholipid antibodies are directed against phospholipid binding proteins such as b2 glycoprotein and prothrombin and are associated with predominantly focal manifestation of NP-SLE. These are transient cerebral ischemia, seizure, chorea, transverse myelitis and cognitive dysfunction. The basic pathologic mechanism being thrombosis within the vessel of a different caliber and subsequent cerebral ischemia.

Clinical manifestations- N.P – SLE

Headache: Prevalence – 24-72%
Headache occurs with other features of active SLE
Headache can be a component of active SLE in an individual patient
Headache could be unrelated to lupus

**Psychosis, mood disorder and anxiety**

**Psychosis is reported in 8 %**
Characterized by delusions or hallucination (auditory)
Lupus psychosis should be distinguished from steroid induced psychosis, or INH induced if patient is on AKT.
Anxiety depression 29-57%

**Cerebrovascular disease**
Cerebrovascular disease 5-18%
Secondary to atherosclerosis or prothrombotic state due to antiphospholipid Antibodies, hypertension, steroid therapy

**Seizures**
General / focal seizure- 6-51%
Due to generalized disease or focal neurlogic events

**Focal NP-SLE**
Demyelination, transverse myelopathy, chorea:
Rare – Manifestation
Incidence – 1-3%

Demyelination may represent a concordance or overlap of few autoimmune conditions. Transverse myelopathy and chorea present as acute manifestations and have strong association with APLA. Tranverse myelopathy is always secondary to vascular occlusion.

Sensory motor neuropathy has incidence 28% Persistent abnormality due to involvement of small nerve fibers.

**Diagnostic imaging for NP- SLE**

Imaging aims to assess

1. brain structure
2. brain function

- **C.T** - Only for acute cerebral hemorrhage.
- **MRI** – T2 weighted images- to identify edema in NP – SLE

Fixed lesions in paraventricular and sub cortical white matter within the territory of major cerebral blood vessel.

Larger lesion occurring in corpus callosum are characteristics of MS

**Diffuse NP-SLE**

Transient sub cortical white matter lesions,

Patchy hyper intensities in gray matter.

These are not in the territory of major cerebral blood flow.

**Other lesions**

Venous thrombosis
Cerebral infraction
Increase signals in spinal cord of myelopathy
Brain arteriopathy

**PET:** Most objective investigation

**SPECT:** Poor man’s pet analysis. Semiquantitative analysis of reginal cerebral blood flow and metabolism

Findings not specific for SLE

Exquisitively sensitive

Reflects primary or secondary reduction in blood flow

**PET:** PET detects abnormalities in glucose metabolism

**MRA** – Permits non invasive visualization of flow in small caliber vessels (primarily involved in NP-SLE)

**MRS** - Allows identification and quantification of brain metabolites Indirect assessment of cellular changes by [N-acetyl] compounds Neurocognition dysfunction is associated with reduced N-acetyl levels Brain lactate levels are increased indicating ischemic inflammation Choline compounds are increased reflecting damaged cell membranes, myelin destruction

**MTI** – For qualification of diffuse brain damage.
Biologic markers in CSF in NP- SLE

Pleocytosis
Elevated proteins
Elevated Neurofilament triplet protein- 74% sensitive
65% specific
CSF- Gilal fibrillary acidic protein (GFAP)- 48% sensitive
87% specific
NFL/GFAP- levels associated with MRI abnormalities and decreased following T/T with cyclophosphamide.

Diagnosis and Management of N.P SLE

Important step in the management of NP- SLE is to determine whether the event can be convincingly attributed to SLE. So assess the patient to rule out the complications of the disease or its therapy. Correct diagnosis is derived from a careful analysis of the clinical, laboratory and imaging data on a case to case basis. Most useful diagnostic tests are haematology, renal, biochemical and immunological profile and assessment of urinary sediments. Low Hb%, high ESR, low C3 C4 levels, rising titers of dsDNA and active urinary sediments indicate a renal flare. On many occasions CNS and renal flare occur simultaneously CSF study to rute out infections such as tuberculosis and India ink preparation for fungi is the next important step in a patient with NP-SLE. Amongst the panel of autoantibodies in a patient with seizures, stroke, chorea or transverse myelitis antiphospholipid antibody estimation provides highest diagnostic yield and enforces therapeutic implications with anticoagulants.

Neuro imaging to assess brain structure and function should be ordered as per the clinical scenario.

Steroid and hydroxychloroquine induced psychosis may present in a similar fashion as disease relapse. Increasing steroid dose will reduce manifestations due to relapse but will worsen in case of steroid induced psychosis. Primary CNS manifestation in an undiagnosed patient poses difficulty in diagnosing SLE but diagnosing CNS lupus in a known case of SLE is comparatively easy.

Management of Neuro Psychiatric events in SLE

Establish the diagnosis of NP-SLE.

Identify and treat potential aggravating factors such as
1. Hypertension
2. Infection
3. Metabolic abnormalities  
   | Hyponatremia |
   | Hypoglycemia   |
   | Hypocalcaemia  |
Initiate symptomatic therapy with
   | Anticonvulsants |
   | Psychotropics  |
   | Anxiolytics    |
Specific therapies
   | Immunosuppression |
   | Corticosteroids  |
The treatment of NP-SLE is emperic for diffuse CNS manifestations. Injectable methyl prednisolone 1 gm daily x 3 days followed by Inj cyclophosphomide 1 gm on 4th day is a standard protocol to initiate the immuno suppression. Oral cortico steroids 1 mg/kg recommended as maintenance therapy along with 1 gm CYC monthly for 6 months and 3 monthly for 8 cycles. Maintainance with azathioprine is recommended on completion of induction with CYC. Anticoagulation is indicated strongly for focal disease and such a therapy will be lifelong. Cognitive assessment and intervention is beneficial on a long term. Plasmapheresis is indicated in CNS manifestations secondary to thrombotic thrombocytopenia. I.V.I.G is reserved in non responders to standard protocol or terminally ill patients.

**Suggested Reading**

Medicine Update
Volume 18, 2008

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