"L" for Lupus (Systemic lupus erythematosus)

What is Systemic lupus erythematosus?

Systemic lupus erythematosus (SLE) is a systemic autoimmune rheumatic disease characterized by autoantibody production and protean organ system manifestations. Autoantibodies in SLE are directed against intracellular targets; antinuclear antibodies (ANAs) are the most characteristic and are present in at least 95% of patients with SLE.

What is childhood onset SLE? How does it differ from its adult counterpart?

-The gender distribution of c SLE is 4.5-5:1 (F:M) in contrast to 9:1 to 10:1 in the adult population.

-Age of onset younger than 18 years.

-c SLE is a more aggressive disease with a higher frequency of major organ (renal, neuropsychiatric, etc) involvement

-More frequent use of immunosuppression, increased damage accrual and higher mortality.

- Lastly special needs such as growth monitoring, adolescence issues, adherence and transition to adult care need to be addressed in the comprehensive management of c SLE.

How common is SLE in children?

The prevalence of SLE is lower in children (2 to 26/100,000) compared with adults (20 to 150/100,000). cSLE accounts for about 10- 20% of all cases of SLE. The mean age at onset of cSLE is 12 years; onset below the age of 5 years is distinctly rare and should prompt consideration of monogenic lupus.

What is the etiology of SLE?

The pathophysiology of SLE is complex with genetic, epigenetic, sex and environmental (ultraviolet radiation, infectious agents, drugs, etc) factors interacting to produce widespread immune system dysregulation involving both adaptive and innate immunity, resulting in tissue damage.

What is monogenic lupus? When should a pediatrician think of it ?

Monogenic lupus refers to SLE patients who carry high-penetrance either dominantly or recessively inherited pathogenic variants in a single gene (encoding complement pathways /interferons etc).
Monogenic lupus should be considered with young age at onset (< 5 years), severe or refractory skin disease, history of recurrent infections and in the setting of consanguinity.

What is drug-induced lupus ?

- Drug-induced lupus (DIL) refers to the presence of SLE manifestations occurring following exposure to specific medications in individuals without prior history of SLE.
- Medications commonly implicated in DIL are procainamide, hydralazine, penicillamine, quinidine, isoniazid, minocycline, methyldopa, anti-TNFα agents and IFNα.
- Severe nephritis and central nervous system (CNS) involvement are rare in DIL, as are the presence of anti-double-stranded DNA (anti-dsDNA) antibodies and hypocomplementemia.

How does SLE manifest in children?

c-SLE can manifest with protean clinical and laboratory manifestations. The most common presenting features include fever, malar rash, arthritis, cytopenias, glomerulonephritis and neuropsychiatric disease. The common clinical manifestations are summarized **(Table- 1)**

Table-1: Clinical manifestations of Systemic Lupus Erythematosus

Organ system	Common manifestations
Mucocutaneous	**Lupus erythematosus (LE)- specific skin lesions-** **Acute cutaneous LE (ACLE)-** localized (malar rash) or generalized **Subacute cutaneous LE (SCLE)-** annular or papulosquamous **Chronic cutaneous LE (CCLE)**- Discoid lupus erythematosus, lupus panniculitis/ profundus, chilblain lupus **LE- non-specific**- Raynaud's phenomenon, livedo reticularis, non-scarring alopecia, vasculitis (leukocytoclastic vasculitis), erythema multiforme (Rowell's syndrome) Mucosal ulcers- oral, nasal
Musculoskeletal	Arthralgia, arthritis- typically symmetric, affecting knees, wrists, and small joints of hands/ Jaccoud's-like arthropathy (reducible deformities, absence of erosions, due to ligamental and/or joint capsule laxity Myalgia, myositis Avascular necrosis, Osteoporosis
Hematological	Anemia (anemia of chronic disease, autoimmune hemolytic, microangiopathic hemolytic anemia), leukopenia, thrombocytopenia, thrombotic thrombocytopenic purpura (TTP)
Renal	**Lupus nephritis (LN)- ISN/ RPS classification-** **Class I**- Minimal mesangial LN **Class II**- Mesangial proliferative LN **Class III**- Focal proliferative LN **Class IV**- Diffuse proliferative LN **Class V-** Membranous LN **Class VI**- Advanced sclerotic LN
Nervous system	**Central nervous system-** Aseptic meningitis, cerebrovascular disease, Demyelinating syndrome, Headache, Movement disorder, Myelopathy, Seizure, Acute confusional state, Anxiety disorder, Cognitive dysfunction, Mood disorder, Psychosis **Peripheral nervous system-** Guillain- Barre syndrome, Mononeuropathy, Polyneuropathy, Myasthenia gravis, Cranial neuropathy
Pleuropulmonary	Pleuritis, pleural effusion, acute lupus pneumonitis, diffuse alveolar hemorrhage, chronic interstitial lung disease, pulmonary arterial hypertension
Cardiovascular	Pericarditis, myocarditis, valvular abnormalities- Libman- Sacks endocarditis
Constitutional	Fever, weight loss, fatigue

ISN- International Society of Nephrology, RPS- Renal Pathology Society

When does a pediatrician suspect SLE in OPD ?

Common scenarios where one should think of SLE are

- **A**dolescent ,**A**lopecia, **A**rthritis, **A**nemia(especially hemolytic)
- **B**utterfly rash
- **C**utaneous – Hsp like rash, gangrene ,Raynauds phenomenon, livedo, Mucositis, **C**ytopenias, **C**horea
- **D**rug hypersensitivity like situation with inflammation, **D**rugs causing DLE
- **E**levated **ESR** with **N**ormal **CRP**
- **F**evers of unknown origin , Severe **F**atigue and **F**altering weight
- **G**irls with unexplained systemic inflammation
- **H**ard palate ulcers, **H**emophagocytic lymphohistiocytosis (**H**LH)
- ***H****igh index of suspicion when labelling a child as autoimmune hemolytic anemia (AIHA) , chronic ITP, Evans syndrome , unusual age of nephritis /nephrotic , unexplained CNS manifestations ,unexplained bleeding (menorrhagia), thrombotic events against a backdrop of inflammation is warranted .*
  Ruling out SLE is paramount in these situations .
- **I**nflammation (unexplained systemic inflammation) suggested by relevant clinical scenarios
- **L**ymphadenopathy**, L**eucopenias **,L**ymphopenias

How to work up a child with suspected SLE?

- The diagnosis of cSLE is clinical (based on detailed history, meticulous physical examination) and supported by laboratory studies and tissue biopsy when required.
- Laboratory investigations include hemogram, hepatic and renal function, direct Coombs test, serum complement (C3 and C4) levels, anti-nuclear antibodies (ANA), anti–dsDNA, antibodies to the extractable nuclear antigens (Ro/SS-A, La/SS-B, Smith, and ribonucleoprotein [RNP]), antiphospholipid antibodies and urinalysis.

In a suspected clinical setting , recognition of anemia , leucopenia (lymphopenia), thrombocytopenia , negative CRP and a high ESR are often early clues to possible SLE .

These should lead to screening (ANA ,C3, C4,urine PC ratio) followed by tests to confirm SLE.(ANA Blot)

Anti -ds DNA and anti -Smith antibody are extremely specific to diagnose SLE.

Interpretation of ANA BLOT to be done with regards specific context / consultation with the pediatric rheumatologist.

Once confirmed , documentation of internal organs is extremely important .

Assessment of organ damage

Kidney Biopsy - Abnormal urinalysis (proteinuria, glomerular hematuria, cellular casts) or reduced renal function.
EYE check- Visual acuity, Retinal vasculitis , scleritis , color vision and field of vision
Liver function tests
Thyroid function tests
Other organs based on involvement patterns (CNS /CVS/GI etc)

Clinical Pearls

- ***Recognise based on clinical and suggested basic laboratory patterns scale***
- ***Screen using ANA (by immunofluorescence), Serum C3, C4 levels and urine PC ratio***
- ***Confirm using ANA Blot***
- ***Document organ involvement***
- ***Referral to pediatric rheumatologist (Proceed with management)***

How do you treat SLE in children?

- **Glucocorticoids (GC)** are one of the main therapeutic agents for SLE and the most useful drugs for the rapid induction of remission in the setting of active disease. In severe disease, intravenous pulse methylprednisolone is administered at a dose of 10-30 mg/kg (max-1 gm/dose) daily for 3-5 days, followed by oral prednisolone at 1-2mg/kg/day (max- 60mg daily) according to the severity of organ involvement.
- Early Addition of **steroid-sparing agents** (azathioprine, mycophenolate, cyclophosphamide, rituximab, belimumab, etc.) especially in moderate to severe disease to control the disease activity and facilitate tapering of GC .
- **Hydroxychloroquine (HCQ)** (5 mg/kg/day, max- 400 mg/day) is used as background therapy in all patients unless contraindicated.
- Vit D and calcium supplements .
- Thyroid supplements and low dose aspirin as indicated by suggestive tests
- Sun protection measures (use of sun screen lotion SPF atleast 25) , avoidance of sun from 10 am to 5 pm , use of full hats , full sleeved clothes form an important part of advice
- **Additional vaccinations ,care of intercurrent infections form an important aspect of pediatric care in liason with the primary subspecialist .**

Take home messages

- **Think of lupus to diagnose lupus -Recognition of clinical pattern crucial**
- **Inflammatory backdrop**
- **Female ,Fevers, Fatigability ,Constitutional features often the presenting symptoms**
- **Malar rash, Hard palate ulcers ,mucocutaneous lesions often a clue**
- **Unexplained Anemias/Cytopenias/Evans syndrome /Nephritis/Encephalopathy**
- **Negative CRP, Elevated ESR**
- **Screen with ANA (IF), C3, C4 ,Spot Urine PC ratio**
- **Confirm with ANA Blot ,document organ involvement.**
- **Early referral to pediatric rheumatology care and Management in liason with the subspecialist**

Next Coming ‘M’ for Macrophage activation syndrome

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