▌▌ REVIEW ARTICLE ▌▌

Lupus erythematosus: A pediatric perspective

Keshavmurthy A Adya, Arun C Inamadar, Aparna Palit

Department of Dermatology, Venereology and Leprosy, Shri BM Patil Medical College, Hospital and Research Center, BLDE University, Bijapur, Karnataka, India

ABSTRACT

Lupus erythematosus (LE) is an autoimmune multisystem disorder with varied clinical manifestations. There are many similarities and differences between pediatric and adult disease in regard to epidemiological, clinical and therapeutic aspects. In general, the disease in children has a more aggressive course and need for prolonged treatment is frequent, which implies a greater incidence of therapy-related adverse effects. This review addresses various aspects of pediatric LE and how they differ from or are similar to adult disease.

Key words: Childhood LE, neonatal LE, Autoimmune multisystem disorder

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune multisystem disease characterized by production of autoantibodies and deposition of complement-fixing immune complexes in various tissues, resulting in their damage. In patients with SLE, a multitude of antibodies are produced that include many "organ-specific" ones that target their respective tissues producing a wide range of clinical manifestations, which are characterized by remissions and exacerbations. There are several similarities as well as differences between pediatric and adult-onset lupus erythematosus (LE) in regard to etiology, clinical manifestations, complications and prognosis. LE in the pediatric age group represents both a special challenge and a special opportunity. Early onset allows observation of the natural history of the disease and investigation of potential etiologies, free from confounding factors that are frequently present in older patients.[1]

EPIDEMIOLOGY

The true incidence and prevalence of pediatric LE are still unknown.[2] Although better numbers have been provided by countries where every child with a specific diagnosis is reported to a central registry, these countries have lacked the ethnic diversity that is found in larger countries, making their data inapplicable. Because of such difficulties in assessing the incidence of SLE, the prevalence can only be estimated.[3] The influences of sex and racial origin on the occurrence and manifestations of SLE are widely recognized.[4-7] In childhood, the influence of race is striking. The age and sex-adjusted prevalence of SLE in African American, Asian and Hispanic children were more than three-fold that of white children at one large center.[4] The same study found a 60% increase in the frequency of post-pubertal SLE compared with pre-pubertal SLE in male children. The corresponding figures for females were a 246% increase in white female children, 434% in African American females, 406% in Asian females and 181 in Hispanic females.

ETIOPATHOGENESIS

The exact cause of SLE is unknown. LE can best be described as a disorder in which the interplay between host factors (genetic factors, hormonal factors, etc.) and environmental factors (ultraviolet [UV] radiation, viruses, drugs, etc.) leads to loss of self-tolerance and induction of autoimmunity, which is followed by activation of the immune system with subsequent immunological injury to the end organs.[8]

ADDRESS FOR CORRESPONDENCE
Dr. Arun C Inamadar,
Department of Dermatology, Venerology and Leprosy, Shri BM Patil Medical College, Hospital and Research Center, BLDE University, Bijapur - 586 103, Karnataka, India.
E-mail: aruninamadar@rediffmail.com

Access this article online	
Quick Response Code	**Website:**

GENETIC FACTORS

Considerable evidence support the role of genetic factors in the pathogenesis of LE.[9] The condition has been reported in identical twins,[10,11] with a concordance rate of 65%.[11] The onset of SLE in identical twins occurred within 2 years, compared with an interval of 9 years between siblings and 20 years between parents and offspring.[12]

AUTOANTIBODIES

Non-organ-specific humoral autoantibodies are the hallmark of SLE. A host of autoantibodies are found in LE, among which some are more disease specific (anti-double-stranded DNA and anti-Sm antibodies) and some are much more commonly found (antinuclear and anti-Ro antibodies). Disease could be produced by the development of such antibodies against tissue antigens to which tolerance has been lost by failure of homeostatic immunological mechanisms.[13,14] Anti-Ro or closely related antibodies are associated with neonatal lupus erythematosus (NLE) and possibly in other childhood SLE. Antiphospholipid autoantibodies are also frequently found in children with SLE and in their family members.[15-17]

IMMUNOLOGIC ABNORMALITIES

Childhood SLE is more frequently associated with immunological abnormalities. Complement deficiency[18] (especially C2 or C4 deficiency) and IgA deficiency[19] are the frequent findings in childhood SLE.

ENVIRONMENTAL FACTORS

Current evidence suggests that environmental factors like UV radiation, viruses (especially Epstein-Barr virus),[1] drugs, etc. may produce altered immunological response in a genetically predisposed individual and lead to development of the disease.

CLINICAL FEATURES

Dermatologic Manifestations
All the cutaneous lesions of LE are induced or exacerbated by UV radiation, but definite photosensitivity is seen in about 16% of childhood SLE.[20] The typical butterfly rash is seen only in 30–50% of childhood SLE.[21] This rash is frequently associated with vasculitic involvement of hard palate, which serves as a useful confirmatory sign.

Discoid lupus erythematosus is uncommon in childhood. There appears to be no female preponderance, there is less photosensitivity and the frequency of progression to systemic disease is higher. The other clinical features are similar to those in adults.[22]

Other dermatologic manifestations of LE in childhood include recurrent urticaria, bullous lesions and vasculitic lesions like nodules or ulceration, with the latter being associated with active disease. Bullous lesions may resemble bullous pemphigoid and are found more commonly in boys.[23]

Systemic Manifestations
Unexplained fever, malaise and weight loss are the most common systemic features of SLE in childhood and adolescents. These symptoms, especially in the context of an otherwise unexplained anemia and/or thrombocytopenia, should prompt a thorough investigation for LE in this age group. Other systemic manifestations are described in Table 1. A higher frequency of aggressive renal disease, and thus a higher requirement for steroids and immunosuppressive drugs, has been reported among children with lupus compared with their adult counterparts.[3]

LABORATORY EVALUATION

No laboratory findings are unique to SLE in childhood. Hypogammaglobulinemia, pancytopenia, a positive antinuclear antibody (ANA) test, organ-specific and non-organ-specific autoantibodies and other abnormalities are found in a similar manner as in adults. Positive ANA tests may also be found in children with juvenile rheumatoid arthritis and in normal healthy children. The titers of the ANA are generally higher in those with SLE.[3] Antibodies to ribosomal P protein, previously implicated in SLE-associated psychosis and depression, have been shown to be more prevalent in childhood compared with adult-onset SLE. A recent cluster autoantibody analysis study conducted in Toronto reported an increased prevalence of anti-U1RNP and anti-Sm antibodies within non-Caucasian populations. The same study identified three clusters of autoantibodies (anti-dsDNA, anti-dsDNA+antichromatin+antiribosomal P+anti-U1 RNP+anti-Sm+anti-Ro+anti-La and anti-dsDNA+anti-RNP+anti-Sm) associating with different clinical courses (mild disease with no major organ involvement, high frequency of nephritis/serositis/hemolytic anemia and NP disease/nephritis, respectively).[30]

Table 1: Systemic manifestations in childhood LE

System	Manifestations	Remarks
Renal	Hematuria, proteinurea, hypertension, facial and pedal edema	Renal involvement occurs in 2/3rds of cases, which ranges from mild glomerulonephritis to sudden renal failure. However, in children, the signs of renal involvement are frequently silent
Central nervous system	Psychosis, personality changes, seizures, chorea, transverse myelitis, peripheral neuropathy, pseudomotor cerebri	Subtle CNS changes like impaired judgment and poor short-term memory are the most common manifestations. Chorea is more frequent in children compared with adults. Small foci of high signal concentrated in subcortical and/or perivetricular white matter are the most common MRI findings of brain scans[24]
Pulmonary	Pleurisy, pleural effusion, pneumonia, pneumothorax, pulmonary hypertension, pulmonary hemorrhage and chronic restrictive lung disease	Pleurisy and pleural effusion are the most common pulmonary manifestations. The most common fatal complication is pneumonia. A restrictive pattern of pulmonary dysfunction, with characteristically reduced diffusing capacity, not necessarily correlating with symptoms or with other disease manifestations, is the most prevalent lung function test abnormality in both adults and children with SLE[25]
Musculoskeletal	Non-erosive arthritis, avascular necrosis	Non-deforming arthritis develops at some point in over 80% of children with SLE. Significant arthritis involving the small joint of the hands and feet is seen in 40–60%
Cardiac	Pancarditis, Libmann-Sacks endocarditis, flow murmurs, coronary arteritis, premature myocardial infarction	Cardiac manifestations are rarely prominent and are generally asymptomatic. Most children are anemic and develop flow murmurs. A study by Gazarian et al,[26] showed that pediatric patients with lupus exhibit a considerably high prevalence of asymptomatic myocardial ischemia. This is because of associated lipid abnormalities
Gastrointestinal	Chronic abdominal pain, hepatomegaly, splenomegaly, pancreatitis, functional asplenia, treatment-associated GI complications	Chronic abdominal pain, anorexia and weight loss are the most common manifestations. More often, pain abdomen is the result of pancreatitis, which may be due to the disease itself or due to steroids or both. Drug-induced GI irritation is frequent and aspirin-induced hepatotoxicity is particularly common
Hematologic/ serologic	Anemia, leucopenia, thrombocytopenia, lupus anticoagulant, anticardiolipin antibodies	Anemia (microcytic) is the most common manifestation. Menorrhagia may be the initial manifestation due to the lupus anticoagulant in teenage females. They are associated with increased risk of thrombosis and CNS disease. It has been estimated that 20–30% of children with idiopathic thrombopenic purpura and positive antinuclear antibodies will eventually develop lupus[27]
Antiphospholipid syndrome	Anemia, thrombocytopenia, recurrent venous and arterial thromboses, skin and neurological complications	Livedo reticularis, heart valve disease and pulmonary hypertension are less common in children than in adults with APS.[28] Pediatric patients with secondary APS tend to be older and exhibit a higher frequency of venous versus arterial thrombotic events associated with skin and hematological manifestations compared with children with primary APS[29]

CNS - Central nervous system; GI - Gastrointestinal; APS - Antiphospholipid syndrome; SLE - Systemic lupus erythematosus

Table 2: Drugs used in the management of childhood LE

Drugs	Dosage	Indications and remarks
NSAIDs	Naproxen 10–15 mg/kg BID in divided doses Diclofenac 1–3 mg/kg BID in divided doses Tolmetin 20–40 mg/kg BID in divided doses Ibuprofen 20–40 mg/kg TID or QID in divided doses	For arthritis and musculoskeletal manifestations
Antimalarials	Hydroxychloroquine sulfate 3–7 mg/kg/d (maximum of 400 mg/d)	For rash, musculoskeletal symptoms and other milder manifestations • Their long-term use has a steroid-sparing effect and HCQS has shown to reduce thrombotic events. • Baseline and half-yearly ophthalmic monitoring for retinal changes is necessary
Corticosteroids	Prednisone 1–2 mg/kg/d Methylprednisolone 30 mg/kg/d (intravenous pulse) for 3 days (up to a maximum of 1 g)	For patients with severe renal, CNS or hematological manifestations • Generally, daily prednisone regimen is practiced, starting with higher doses (up to 5 mg/kg/d) and gradual tapering as per the therapeutic response • Intravenous (IV) methylprednisolone pulse is given to combat acute renal or CNS flares • Alternatively, low-dose daily prednisone (0.5 mg/kg/d) may be used in conjunction with intermittent high-dose IV methylprednisolone weekly
Non-steroidal immunosuppressive drugs	Cyclophosphamide 0.5–1 g/m^2/month for 7 m and then every 3 months for an additional 30 months Methotrexate Azathioprine Mycophenolate moftil	• Cyclophosphamide is used for class IV and in some cases of class III nephritis. It may be used in conjunction with corticosteroids. It has also been used in CNS disease with variable results • MMF (up to 1 g BID) is a safer alternative for lupus nephritis, especially in children with moderate disease but with persistent hypocomplementemia • In patients not responding to standard monthly cyclophosphamide or those with severe recurrences, IV cyclophosphamide may be combined with high-dose IV MTX (300 mg/m^2) • Azathioprine is used for milder degrees of nephritis

MTX - Methotrexate; LE - lupus erythematosus; MMF - Mycophenolate moftil; HCQS - Hydroxychloroquine sulfate

TREATMENT

Pediatric SLE has a more aggressive course, with increased incidence of renal and central nervous system disease. Hence, the use of higher doses of corticosteroids for longer duration is more frequent in this age group than in adults. Table 2 outlines the various drugs used in the management of LE in childhood.[3] Milder manifestations are managed by non-steroidal anti-inflammatory drugs and antimalarials. In the presence of severe disease manifestations, corticosteroids and immunosupressives (especially for nephritis) are used. Other modalities include monoclonal antibodies, autologous stem cell transplantation[31] and intravenous immunoglobulin. As regards monoclonal antibodies, rituximab is currently being used in immune thrombocytopenia and rheumatoid arthritis in children, and its therapeutic role in SLE is being investigated.

NEONATAL LUPUS ERYTHEMATOSUS

NLE is a disorder thought to be caused by the transplacental passage of maternal antibodies. It is characterized by transient skin lesions resembling subacute cutaneous LE and/or congenital heart block (CHB), occurring in the babies of mothers with clinical or subclinical autoimmune connective tissue disease and associated with the transplacental passage of maternal autoantibodies to the ribonucleoproteins (RNPs), Ro-SSA, La-SSB or U1-RNP.[32] A considerable proportion of mothers of affected infants are asymptomatic (40%).[33]

ETIOPATHOGENESIS

Among the above-mentioned transplacentally transferred maternal autoantibodies, the Ro-SSA is associated with 95% of NLE.[33,34] In cases where only anti-U_1RNP antibodies are found, only cutaneous disease has been reported.[33] Two main Ro/SS-A proteins exist (52 and 60 kDa), and studies suggest the former being frequently found in CHB,[35,36] whereas the latter is more frequently associated with cutaneous disease.[37] The presence of Ro and La antigens has been demonstrated in fetal skin and cardiac-conducting tissue.[38,39] The antibodies bind to the antigens at these sites after which a sequence of apoptosis, opsonization and fibrosis follows.[40]

CLINICAL FEATURES

About 90% of neonates have skin lesions, and both skin and cardiac lesions are seen in 10%.[41,42] In about two-thirds of NLE with skin lesions, the lesions are present at birth,[43,44] and, in the remainder, they may appear later as the 5th month.[41] But, generally, the lesions appear within the first 2 months of life and resolve within 4–6 months with disappearance of maternal antibodies.

Cutaneous

An erythematous, scaly eruption on the face and periorbital skin (raccoon sign) is the most common cutaneous finding in NLE, with the scalp, trunk, extremities, neck and intertriginous involvement occurring in decreasing order of frequency.[45] The eruption may be aggravated by UV exposure, and there are reports of the rash being triggered by phototherapy for neonatal jaundice.[46,47] The rash may sometimes be present at birth, when it becomes difficult to implicate UV exposure as the etiology.[48] Other manifestations include a vitiligo-like eruption,[49] morphea-like lesions[50] and papules on the feet.[51] Occasionally, NLE presents as extensive reticulate erythema with atrophy, closely resembling cutis marmorata telangiectatica congenita.[52,53] In most cases, the lesions resolve within a year. Occasionally, atrophy, telangiectasia and scarring may remain as residua.

Cardiac

The incidence of CHB in the offspring of anti-Ro-positive women is 1–2%, and the risk of recurrence of complete atrioventricular (AV) block is almost 10-times higher in the following pregnancies. Substantial morbidity (65% require lifelong pacing) and mortality (20%) are associated with CHB.[54] Associated features may also include pericardial effusions, pleural effusions, ascites, intrauterine growth retardation and hydrops fetalis.[55] Dilated cardiomyopathy occurs in up to 20%, and has a significant mortality in the first year of life.[56]

Other Systemic Manifestations

A smaller proportion of infants have combinations of hepatomegaly, splenomegaly, lymphadenopathy, autoimmune hemolytic anaemia, thrombocytopenia and pneumonitis, which are generally mild in degree and fairly transient.

TREATMENT

Cutaneous lesions are transient and generally resolve without any residua. However, photoprotection is necessary. Up to 50% of patients with heart blocks may require pacing in the newborn period, and others may require pacemaker insertion at a later date.[55]

PREVENTION

Serial echocardiograms to detect early fetal abnormalities, such as premature atrial contractions or moderate pericardial effusion, which might precede complete heart block and obstetric sonograms performed biweekly starting from the 16th week of gestational age in the presence of anti-Ro/SSA antibodies, seems to be the best current recommendation.[57] Effective management of these early fetal cardiac abnormalities may prevent the development of complete AV block. Intravenous immunoglobulin had been used to prevent the development of CHB in eight high-risk mothers (anti-Ro/SSA positive and previous pregnancy with CHB), and, in one case, CHB recurred (12.5%).[58]

Learning Points

- Pediatric LE represents both a special challenge and a special opportunity. There are several similarities and differences between pediatric and adult-onset LE in regard to etiology, clinical manifestations, complications and prognosis
- True incidence and prevalence of pediatric LE are still unknown. In childhood LE, the influence of race is striking
- Childhood LE is more frequently associated with immunological abnormalities like complement and immunoglobulin A deficiency
- Definite photosensitivity is seen only in 16% of childhood LE, and the typical malar rash is seen in 30–50%. Discoid LE is rare in childhood
- Fever, malaise and musculoskeletal pains are the most common manifestations of childhood LE. Renal involvement is seen in 2/3rds of the cases
- Neonatal LE is a rare condition seen in neonates born to mothers with antibodies against Ro/SSA, La/SSB or U_1RNP. It is characterized by transient photosensitive rash, and, in about 10%, heart blocks
- In general, pediatric LE has a more aggressive course. The use of higher doses of corticosteroids for a longer duration is more frequent in this age group than in adults
- Systematic use of cyclophosphamide and other safer alternatives like MMF, azathioprine, etc., has significantly improved the prognosis of children with LE
- Newer management options like stem cell therapy, monoclonal antibodies, etc., may promise a brighter tomorrow to these patients with regard to the survival and quality of life

REFERENCES

1. James JA, Kaufman KM, Farris AD, Taylor-Albert E, Lehman TJ, Harley JB. An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. J Clin Invest 1997;100:3019-26.

2. Singsen BH. Epidemiology of rheumatic diseases: Rheumatic diseases of childhood. Rheum Dis Clin North Am 1990;16:581-99.

3. Thomas J, Lehman A. Systemic Lupus Erythematosus in Childhood and Adolescence. In: Wallace DJ, Hahn BH, editors. Dubois' Lupus Erythematosus. 7th ed. Chapter 43. Philadelphia: Lippincot Williams and Wilkins; 2007. p. 848-69.

4. Lehman TJ, McCurdy D, Spencer C. Prognostic value of antibodies to Ro/SSA, SSB/La, and RNP in children with systemic lupus erythematosus (abstract). Arthritis Rheum 1990;33(Suppl):S154.

5. Segel M, Lee SL. The epidemiology of systemic lupus erythematosus. Semin Arthritis Rheum 1973;3:154.

6. Sequeira W, Polisky RB, Alrenga DP. Neutrophilic dermatosis (Sweet's syndrome). Association with a hydralazine-induced lupus syndrome. Am J Med 1986;81:558-60.

7. Gedalia A, Molina JF, Molina J, Uribe O, Malagon C, Espinoza LR. Childhood-onset systemic lupus erythematosus: A comparative study of African Americans and Latin Americans. J Nat Med Assoc 1999;91:497-501.

8. Costner MI, Sontheimer RD. Lupus Erythematosus. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, editors. Fitzpatrick's Dermatology in General Medicine. Vol. 2, Chapter 156, 7th ed. USA: The McGraw-Hill Companies; 2008. p. 1515-35.

9. Criswell LA. The genetic contribution to systemic lupus erythematosus. Bull NYU Hosp Jt Dis 2008;66:176-83.

10. Block SR, Winfield JB, Lockshin MD, D'Angelo WA, Christian CL. Studies of twins with systemic lupus erythematosus. Am J Med 1975;59:533-52.

11. Block SR, Lockshin MD, Winfield JB, Weksler ME, Imamura M, Winchester RJ, *et al*. Immunologic observations on nine sets of twins either concordant or discordant for SLE. Arthritis Rheum 1976;19:545-54.

12. Alvarellos A, Ahearn JM, Provost TT, Dorsch CA, Stevens MB, Bias WB, *et al*. Relationships of HLA-DR and MT antigens to autoantibody expression in systemic lupus erythematosus. Arthritis Rheum 1983;26:1533-4.

13. Alarcón-Segoviá D. The pathogenesis of immune dysregulation in systemic lupus erythematosus. A Troika. J Rheumatol 1984;11:588-90.

14. Beck JS, Rowell NR. Discoid lupus erythematosus: A study of the clinical features and biochemcial and serological abnormalities in 120 patients with observations on the relationship of this disease to systemic lupus erythematosus. QJM 1966;35:119-36.

15. Molta C, Meyer O, Dosquet C, Montes de Oca M, Babron MC, Danon F, *et al*. Childhood onset systemic lupus erythematosus: Antiphospholipid antibodies in 37 patients and their first-degree relatives. Pediatrics 1993;92:849-53.

16. Ravelli A, Caporali R, Di Fuccia G, Zonta L, Montecucco C, Martini A. Anticardiolipin antibodies in pediatric systemic lupus erythematosus. Arch Pediatr Adolesc Med 1994;148:398-402.

17. Campos LM, Kiss MH, D'Amico EA, Silva CA. Antiphospholipid antibodies and antiphospholipid syndrome in 57 children and adolescents with systemic lupus erythematosus. Lupus 2003;12: 820-6.

18. Agnello V, DeBracco MM, Kunkel HG. Hereditary C2 deficiency with some manifestations of systemic lupus erythematosus. J Immunol 1972;108:837-40.

19. Cassidy JT, Burt A, Petty R, Sullivan D. Selective IgA deficiency

in connective tissue diseases. N Engl J Med 1969;280:275.

20. Cassidy JT, Petty RE. Textbook of pediatric rheumatology. 2nd ed. New York, NY: Churchill Livingstone; 1990.

21. Glidden RS, Mantzouranis EC, Borel Y. Systemic lupus erythematosus in childhood: Clinical manifestations and improved survival in fifty-five patients. Clin Immunol Immunopathol 1983;29:196-210.

22. George PM, Tunnessen WW. Childhood discoid lupus erythematosus. Arch Dermatol 1993;129:613-7.

23. Lamy P, Valla D, Bourgeois P, Rueff B, Benhamou JP. Primary sclerosing cholangitis and systemic lupus erythematosus. Gastroenterol Clin Biol 1988;12:962-4.

24. Appenzeller S, Rondina JM, Li LM, Costallat LT, Cendes F. Cerebral and corpus callosum atrophy in systemic lupus erythematosus. Arthritis Rheum 2005;52:2783-9.

25. Vitali C, Bencivelli W, Isenberg DA, Smolen JS, Snaith ML, Sciuto M, *et al*. European Consensus Study Group for Disease Activity in SLE. A report of the Consensus Study Group of the European Workshop for Rheumatology Research. Clin Exp Rheumatol 1992;10:527-39.

26. Gazarian M, Feldman BM, Benson LN, Gilday DL, Laxer RM, Silverman ED. Assessment of myocardial perfusion and function in childhood systemic lupus erythematosus. J Pediatr 1998;132:109-16.

27. Schmugge M, Revel-Vilik S, Hiraki L, Rand ML, Blanchette VS, Silverman ED. Thrombocytopenia and thrombembolism in pediatric systemic lupus erythematosus. J Pediatr 2003;143:666-9.

28. Berkun Y, Padeh S, Barash J, Uziel Y, Harel L, Mukamel M, *et al*. Antiphospholipid syndrome and recurrent thrombosis in children. Arthritis Rheum 2006;55:850-5.

29. Avcin T, Cimaz R, Silverman ED, Cervera R, Gattorno M, Garay S, *et al*. Pediatric antiphospholipid syndrome: Clinical and immunologic features of 121 patients in an international registry. Pediatrics 2008;122:1100-7.

30. Papadimitraki ED, Isenberg DA. Childhood- and adult-onset lupus: An update of similarities and differences. Expert Rev Clin Immunol 2009;5:391-403. Available from:http://www.medscape.com/viewarticle/708057_2. [Last accessed on 2009].

31. Wulffraat NM, Sanders EA, Kamphuis SS, Rijkers GT, Kuis W, Lilien M, *et al*. Prolonged remission without treatment after autologous stem cell transplantation for refractory childhood systemic lupus erythematosus. Arthritis Rheum 2001; 44:728-31.

32. Petri M, Watson R, Hochberg MC. Anti-Ro antibodies and neonatal lupus. Rheum Dis Clin North Am 1989;15:335-60.

33. McKinlay JR, Cooke LM, Cunningham BB, Gibbs NF. Neonatal Lupus Erythematosus. J Am Board Fam Med 2001;14. Available from: http://www.medscape.com/viewarticle/405824_3. [Last accessed on 2001].

34. Franco HL, Weston WL, Tan E. Association of antibodies to sicca syndrome antigens in newborns with lupus erythematosus and their mothers. Clin Res 1980;28:134A.

35. Viana VS, Garcia S, Nascimento JH, Elkon KB, Brot N, Campos de Carvalho AC, *et al*. Induction of *in vitro* heart block is not restricted to affinity purified anti-52 kDa Ro/SSA antibody from mothers of children with neonatal lupus. Lupus 1998;7:141-7.

36. Eftekhari P, Sallé L, Lezoualc'h F, Mialet J, Gastineau M, Briand JP, *et al*. Anti-SSA/Ro52 autoantibodies blocking the cardiac 5-HT4 serotoninergic receptor could explain neonatal lupus congenital heart block. Eur J Immunol 2000;30:2782-90.

37. Lee LA, Frank MB, McCubbin VR, Reichlin M. Autoantibodies of neonatal lupus erythematosus. J Invest Dermatol 1994;102:963-6.

38. Lee LA, Harmon CE, Huff JC Norris DA, Weston WL. The demonstration of SS-A/Ro antigen in human fetal tissues and in neonatal and adult skin. J Invest Dermatol 1985;85:143-6.

39. Horsfall AC, Venables PJ, Taylor PV, Maini RN. Ro and La antigens and maternal autoantibody idiotype on the surface of myocardial fibers in congenital heart block. J Autoimmun 1991;4:165-76.

40. Buyon JP, Clancy RM. Neonatal lupus: basic research and clinical perspectives. Rheum Dis Clin N Am 2005;31:299-313.

41. McCune AB, Weston WL, Lee LA. Maternal and fetal outcome in neonatal lupus syndrome. Ann Intern Med 1987;106:518-23.

42. Lee LA. Neonatal lupus erythematosus. J Invest Dermatol 1993;100:S9-13.

43. Draznin TH, Esterly NB, Furey NL, DeBofsky H. Neonatal lupus erythematosus. J Am Acad Dermatol 1979;1:437-42.

44. Soltani K, Pacernick LJ, Lorincz AL. Lupus erythematosus-like lesions in newborn infants. Arch Dermatol 1974;110:435-7.

45. Weston WL, Morelli JG, Lee LA. The clinical spectrum of anti-Ro positive neonatal lupus erythematosus. J Am Acad Dermatol 1999;40:675-81.

46. Gawkrodger DJ, Beveridge GW. Neonatal lupus erythematosus in four successive siblings born to a mother with discoid lupus erythematosus. Br J Dermatol 1984;111:683-7.

47. Luo SF, Huang CC, Wang JW. Neonatal lupus erythematosus: Report of a case. J Formos Med Assoc 1989;88:832-5.

48. Cimaz R, Biggioggero M, Catelli L, Muratori S, Cambiaghi S. Ultraviolet light exposure is not a requirement for the development of cutaneous neonatal lupus. Lupus 2002;11:257-60.

49. Jenkins RE, Kurwa AR, Atherton DJ, Black MM. Neonatal lupus erythematosus. Clin Exp Dermatol 1994;19:409-11.

50. Ohtaki N, Miyamoto C, Orita M, Koya M, Matsuo M. Concurrent multiple morphea and neonatal lupus erythematosus in an infant boy born to a mother with SLE. Br J Dermatol 1986;115:85-90.

51. See A, Wargon O, Lim A, Sugo E, Le K. Neonatal lupus presenting as papules on the feet. Australas J Dermatol 2005;46:172-6.

52. Carrascosa JM, Ribera M, Bielsa I, Coroleu W, Ferrándiz C. Cutis marmorata telangiectatica congenital or neonatal lupus? Pediatr Dermatol 1996;13:230-2.

53. Greist MC, Probst E. Cutis marmorata telangiectatica congenita or neonatal lupus. Arch Dermatol 1980;116:1102-3.

54. Friedman DM, Rupel A, Buyon JP. Epidemiology, etiology, detection, and treatment of autoantibody-associated congenital heart block in neonatal lupus. Curr Rheumatol Rep 2007;9:101-8.

55. Saleeb S, Copel J, Friedman D, Buyon JP. Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block: Retrospective review of the research registry for neonatal lupus. Arthitis Rheum 1999;42:2335-45.

56. Eronen M, Siren MK, Ekblad H, Tikanoja T, Julkunen H, Paavilainen T. Short- and long-term outcome of children with congenital complete heart block diagnosed in utero or as a newborn. Paediatrics 2000;106:86-91.

57. Brucato A. Prevention of congenital heart block in children of SSA-positive mothers. Rheumatology 2008;47:iii35-7.

58. Kaaja R, Julkunen H. Prevention of recurrence of congenital heart block with intravenous immunoglobulin and corticosteroid therapy: Comment on the editorial by Buyon *et al*. Arthritis Rheum 2003;48:280-1; author reply 281-2.