REVIEW ARTICLE

Juvenile Systemic Lupus Erythematosus: Review of Clinical Features and Management

S HABIBI, *MA SALEEM AND *†AV RAMANAN

*From the Department of Rheumatology, Nizams Institute of Medical Sciences, Hyderabad, India; *Department of Pediatric Nephrology, Academic Renal Unit, University of Bristol, Bristol and †Department of Pediatric Rheumatology, Honorary Reader, University of Bristol, Bristol Royal Hospital for Children and Royal National Hospital for Rheumatic Diseases, Bath, UK.*

Correspondence to: Dr Athimalaipet Ramanan, Department of Pediatric Rheumatology, Upper Maudlin Street, Bristol Royal Hospital for Children, Bristol, UK, BS2 8BJ. avramanan@hotmail.com

Juvenile systemic lupus erythematous (SLE) is a multisystem autoimmune disorder that is characterized by widespread immune dysregulation, formation of autoantibodies and immune complexes, resulting in inflammation and potential damage to a variety of organs. It is not uncommon for children to present with non-specific symptoms, and little else, and be treated for a presumed infection, including tuberculosis – with subsequent evaluation revealing the diagnosis of lupus, requiring aggressive management. A high index of suspicion must be maintained for the diagnosis of SLE in adolescent children, particularly girls.

About 15-20% of lupus patients, develop their first symptoms before 18 years of age [1-8]. It is slightly more common in girls, with the sex ratio being about 4:3 before puberty; however after puberty, the sex difference increases to about 4:1 [1]. Juvenile SLE is a more aggressive disease than adult SLE, having a substantially higher prevalence and severity of nephritis and CNS disease, requiring higher doses and more sustained need for corticosteroids and other immunosuppressive medications [3,6-9]. Children, especially adolescents, experience a more negative impact on their physical and psychosocial development. Additional issues to be considered include the side effects of corticosteroids such as osteoporosis, growth retardation and poor compliance with drugs.

EPIDEMIOLOGY

The disease is more common in Native Americans, African Americans and Asians [10]. Prevalence rates of juvenile SLE have varied from 4-250 per 100,000 population [11,12]. There is scarce epidemiological data from India on SLE and none on childhood SLE. In one population prevalence study of SLE in North India, a point prevalence of 3.2 per 100,000 was observed [13]. Samanta, *et al*. [14] studied the prevalence of SLE in Whites and Indian immigrants in the UK, and found that lupus was 3 times more common in Indians than in whites, among both males and females. Another study from Eastern India found that 3.9% of all children presenting to a pediatric rheumatology clinic had SLE [15].

DIAGNOSIS

The 1997 modified ACR criteria designed for the classification of patients for epidemiological studies are widely used for diagnosis (***Table* I**) [16]. The presence of four or more criteria increases the sensitivity for the diagnosis of SLE, although this has not been validated. The criteria can evolve over time, and there is a new classification criteria being developed by the American College of Rheumatology (American College of Rheumatology Annual Scientific Meeting, 2009).

CLINICAL FEATURES

SLE ranges from an insidious, slowly progressive,

chronic disease with exacerbations and remissions, to an acute and rapidly fatal disease. Constitutional features such as fever, fatigue, anorexia, myalgias, weight loss are common both at onset and during exacerbations of the disease [3,5,17]. These may be the presenting features of the disease. Children in general tend to have more severe and more aggressive disease than adults, often presenting with major organ involvement especially renal and neurological [3,6-8]. ***Table* II** lists the various clinical features of the disease.

There are notable differences among the manifestations of the disease between children and adults. A study comparing 56 children with juvenile onset SLE and 194 patients with adult onset SLE, found that renal involvement, encephalopathy and hemolytic anemia, were significantly more common in juvenile SLE as compared to adult SLE (62.5% *vs* 36%, $P<0.001$; 20.4% *vs* 5.3%, $P<0.005$, and 38.5% *vs*.13%, $P<0.001$, respectively) [5]. Another study compared 49 children with 130 adults with SLE. They found a higher frequency of cutaneous vasculitis, nephropathy, seizures and discoid lesions and a lower frequency of articular manifestations in children [17]. Data from India on juvenile SLE is scarce. One study, that compared children with adults with SLE found a more severe form of disease in children, with more frequent renal involvement [18]. The gender ratio showed a female preponderance, similar to that seen in adults. However, this study was from a tertiary referral centre, and subject to bias. Another small case series of 20 children from Kerala reported constitutional features as the most common presenting symptoms [19]. Most of these children were referred as "pyrexia of unknown origin" or "idiopathic thrombocytopenic purpura". This suggests that a high index of suspicion must be maintained, so as to diagnose children with SLE early in their disease course.

Nephritis is more common in children as compared to adults, with studies showing that 75-80% of children develop clinically evident nephritis at some point of their illness [5,9,17,20]. Nephritis is not only more frequent, but more severe in children, and is a major determinant of prognosis and mortality. The pathogenesis may include the deposition of immune complexes, leading to an inflammatory response, and also glomerular thrombosis, particularly in patients with anti-phospholipid antibodies.

TABLE I THE 1997 MODIFIED ACR CRITERIA FOR THE CLASSIFICATION OF SLE

Malar (butterfly) rash
Discoid rash
Photosensitivity
Oral or nasal mucocutaneous ulceration
Nonerosive arthritis
Nephritis
Proteinuria >0.5 g/day
Cellular casts
Encephalopathy
Seizures
Psychosis
Pleuritis or pericarditis
Cytopenia
Positive immunoserology
Antibodies to dsDNA
Antibodies to Sm nuclear antigen
Positive antiphospholipid antibodies based on:
(*i*) IgG or IgM anticardiolipin antibodies,
(*ii*) Lupus anticoagulant, or
(*iii*) False positive serological test for syphilis for atleast 6 months, confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
Positive antinuclear antibody test

The most common initial manifestation of nephritis is microscopic hematuria (79%), followed by proteinuria, including nephrotic syndrome (55%). Decreased GFR and hypertension are also seen (50% and 40%, respectively) [21]. However acute renal failure as a presenting manifestation of nephritis is rare (1.4%) [21].

A renal biopsy should be considered in all children with active nephritis, particularly on the first presentation, and is useful to determine both activity and chronicity, and hence guide treatment and prognosis. The International Society of

TABLE II CLINICAL FEATURES OF SLE

Constitutional	Fever, malaise, anorexia, weight loss
Cutaneous	Malar rash, discoid rash, oral ulcerations, alopecia, photosensitivity, generalized rash
Musculoskeletal	Polyarthralgia and arthritis, tenosynovitis, myalgia, myositis, aseptic necrosis, osteopenia
Cardiac	Pericarditis with or without effusion, myocarditis, Libman-Sack endocarditis, accelerated atherosclerosis, coronary vasculitis
Pulmonary	Pleuritis with or without effusion, pneumonitis, shrinking lung syndrome, pulmonary hemorrhage, pulmonary hypertension
Vascular	Raynaud phenomena, livedo reticularis, thrombosis, vasculitis, erythromelalgia
Gastrointestinal	Peritonitis, hepatomegaly, splenomegaly, mesenteric vasculitis, pancreatitis, colitis
Neurologic	Organic brain syndrome, seizures, psychosis, chorea, cerebrovascular accident, neuropathy, cranial nerve palsy, benign intracranial hypertension, anxiety, depression
Renal	Glomerulonephritis, tubulointestitial nephritis, hypertension, uremia

Nephrology/Renal Pathology Society has classified lupus nephritis into 6 classes [22].

The clinical features of lupus nephritis are generally non-specific, including edema, lethargy, hypertension and dark urine. It is often difficult to predict biopsy findings from the clinical picture. In general, children with mesangial lesions (class I or II on biopsy) seldom have clinical evidence of renal disease, although they may have minimal proteinuria and microscopic hematuria. Renal impairment and heavy proteinuria are more commonly correlated with a more advanced or proliferative picture on biopsy (class III or IV on biopsy).

Children with diffuse proliferative nephritis glomerulonephritis (class IV) have hematuria and proteinuria, which may be of nephrotic range, and leads to renal insufficiency in 60% [1]. Hypertension is also common in these children. Children with membranous lesions (class V) have persistent nephrotic syndrome and hypertension in 30% [1]. These children are risk of developing renal vein thrombosis. Children with class VI lesions have evidence of severe glomerular sclerosis, with end stage renal disease [1]. This usually occurs due to untreated or nonresponsive or relapsing diffuse or focal proliferative glomerulonephritis. Transformation from one class to another is another well-known phenomenon depending on disease progression or response to treatment, as is the occurrence of mixed lesions, such as mixed proliferative and membranous lesions [23].

Box 1 lists the different situations when a pediatrician should suspect lupus in a child.

LABORATORY INVESTIGATIONS

There may be evidence of anemia, leukopenia and lymphopenia, thrombocytopenia or thrombocytosis. During acute exacerbations, the ESR may be elevated. CRP elevations are usually not seen in active lupus, except in superimposed serositis, arthritis or infection [24]. Hence in a child presenting with PUO with an elevated ESR but normal CRP, SLE must be considered. Urine analysis may reveal proteinuria, hematuria and cellular casts.

Antinuclear antibody: These are present in the sera of 95-98% children with SLE [25]. ANA negative lupus is an extremely rare entity, being present in 2-5% of children [26]. With the newer immunofluorescence assays utilizing Hep-2 cells, and ELISA techniques, which are extremely sensitive, having a negative ANA in the face of SLE is extremely rare. Therefore this rare diagnosis is ideally made by an expert.

In general, there is no difference between the levels of ANA in children and adults [5]. The titre of ANA as demonstrated by immunofluorescence of Hep-2 cells, ranges from low (1:80) to very high (>1: 5120). Determination of ANA titre alone is not sufficient to diagnose or to monitor SLE. It has a low specificity for the disease, since it may be positive in other conditions including infections, drugs, other autoimmune disorders, or even in normal persons [27, 28]. A study found that 27% of children with positive ANA did not develop SLE when followed for about 7 years [28]. Hence a positive ANA,

BOX 1: When Should a Pediatrician Suspect Lupus?

- Children, especially adolescent girls with non-specific constitutional features like fatigue, fevers, myalgias, arthralgias.
- Constitututional features with evidence of leukopenia, especially lymphopenia.
- Idiopathic thrombocytopenia, with minor constitutional features and a positive ANA. These children are at a higher risk of evolving into lupus.
- No response of a presumed "infection", including tuberculosis to antibiotics and antitubercular thetrapy.
- Arthralgias, rash, fever, weight loss with active urine sediments in an adolescent girl.
- Unexplained multisystem disease.

especially in low titres, in the absence of other clinical manifestations is not sufficient to diagnose SLE.

Anti-dsDNA antibodies: These are highly specific for SLE, and are present in about 61-93% children with active disease, especially active nephritis [3, 5, 6, 17]. However, they may be absent in about 40% children with active lupus, especially if nephritis is not present. Children tend to have anti-dsDNA antibodies more frequently as compared to adults [3, 5]. Relation between the serum levels of anti-dsDNA antibodies and disease activity is controversial [29]. However most studies have shown a relation between active nephritis and the serum levels of these antibodies [5]. Rising titres may predict a flare and warrant closer monitoring of the child [30].

Anti-Smith antibodies are also highly specific for SLE. These are detected in only about 50% of patients [9]. Other antibodies that may be detected include anti-Ro, anti-La, anti-U1RNP, anti-histone and rheumatoid factor [3,5,6,17].

A recent study evaluated antibody patterns in children with SLE in regard to their ethnicity and analyzed their clinical correlations. They found 3 autoantibody clusters. Cluster 1 had anti-dsDNA antibodies. Cluster 2 consisted of anti dsDNA, antichromatin, antiribosomal P, antiU1RNP, anti-Sm, anti-Ro and anti-La antibodies. Cluster 3 consisted of anti dsDNA, anti-RNP and anti-Sm antibodies. Indian children had cluster 2 antibodies, which had a high proportion of nephritis, serositis, renal failure and hemolytic anemia and cluster 3 with more neuropsychiatric disease and nephritis [31].

Serum complement levels can be a useful measure of disease activity. Complement levels are low in about 90% children with active nephritis, and levels rise with treatment [1]. However, congenital complement deficiencies, especially the early complement components are associated with SLE. Hence the levels of these complement proteins may not rise in these congenital deficiency conditions, even though the disease itself is improving. Thus serum complement levels may not always be useful to monitor lupus activity, and therapy must be administered according to the overall clinical status. SLE patients with complete C4 deficiency have predominant skin manifestations and mild renal disease, and usually demonstrate anti-Ro antibodies, with absent anti-dsDNA antibodies [32]. Anti-C1q antibodies have a sensitivity of 44-100% and a specificity of 70-92% in active renal disease; in combination with low C3 and C4 levels, these may be good predictors of renal flares in patients with SLE [33].

NEONATAL LUPUS ERYTHEMATOSUS (NLE)

It is a rare disorder occurring due to the transplacental passage of maternal anti-Ro or anti-La antibodies [34]. The mothers may be healthy or suffering from various connective tissue diseases. Neonatal lupus can affect the skin, heart, liver, hematological system and the central nervous system.

The most clinically significant manifestations of NLE are cardiac, especially congenital AV block, which occurs in 1 in 14,000 live births, 90% of cases due to transplacental passage of maternal antibodies injuring the normally developing heart [35,36]. It

occurs most commonly between 17-24 weeks of gestation, and maybe associated with myocarditis, leading to hydrops and stillbirth [36]. If a mother has anti-Ro antibodies, the incidence of having an offspring with congenital heart block is about 2%, whereas if the mother has an affected child, the risk increases in the subsequent pregnancy by about 10-fold [36]. Hence all these women must be carefully followed with serial echocardiography.

TREATMENT

Juvenile SLE is associated with a higher mortality and lower rates of remission [4]. This is despite an increasing armamentarium of drugs available to treat the disease and its diverse manifestations. The ideal drug, while reducing the disease activity and preventing damage, must allow for normal growth, development and fertility. Treatment must be tailored according to the disease activity and severity, pattern of organ involvement and the number of flares. The different drugs available today include corticosteroids, hydroxychloroquine, immunosuppressives like azathioprine, cyclophosphamide, mycophenolate mofetil and methotrexate, and recently B-cell depleting therapy. However, therapy remains challenging due to an unpredictable disease course, long-term requirement for therapy, and noncompliance.

The various drugs used, dosage and indication in SLE are given in ***Table* III**.

Hydroxychloroquine has effects beyond just disease control in lupus. The Canadian Hydroxychloroquine group evaluated the ability of long term hydroxychloroquine to prevent major flares in quiescent SLE, and found that it has a long term effect against major flares, reducing the risk by 57% [37].There is also high level of evidence that antimalarials increase long term survival of lupus patients, moderate evidence of protection against irreversible organ damage, bone mass loss and thrombosis [38]. In pregnant women also, antimalarials were found to decrease lupus activity, without harming the fetus. There is also some evidence, though not strong, that these drugs have a favourable effect on lipid levels and prevent atherosclerosis. Hence hydroxychloroquine should be given to all lupus patients throughout the course of their illness, irrespective of disease severity and must be continued during pregnancy.

Management of nephritis: There must be aggressive aiming for remission of all disease activity. Treatment regimens are adapted from protocols used in adults. Like malignancy, treatment of proliferative lupus nephritis involves a phase of remission induction and a phase of remission maintenance. High doses of prednisolone, with or without 3-5 pulses of methylprednisolone along with 6 months of cyclophosphamide, given as monthly pulses is used for induction of remission [39,40]. Although randomized control trials on the use of mycophenolate mofetil for induction of remission of nephritis are lacking in children, trials in adults have shown it to be as effective as cyclophosphamide pulses with significantly less side effects. For remission maintenance, azathioprine or more recently mycophenolate mofetil are used [41-43]. Some studies have also shown improvement in proliferative nephritis with the use of cyclosporine and tacrolimus. However, relapses were found to be common after discontinuation [44, 45].

About 9-15% of children with proliferative nephritis progress to end stage renal disease within 5 years [46]. Post-renal transplant, graft survival rates have been reported to be 91% after living donor and 78% after cadaveric transplants, which are comparable to the rates in adults [47,48].

Management of neuropsychiatric manifestations: Majority of children have an excellent response to treatment, with resolution of symptoms. High doses of corticosteroids with immuno-suppressives, most commonly cyclophosphamide given as monthly pulses are the mainstay of therapy [49]. For those children with thrombosis or strokes, anticoagulation is added [50].

B-cell depleting therapy: A variety of B cell targeted therapies are currently under investigation for the treatment of SLE. Rituximab is a chimeric monoclonal antibody against CD20, which is present on the B cells, from the pre-B cell stage to mature B cells, being absent on antibody secreting plasma cells. Despite favourable preliminary reports, clinical trials in adults failed to meet their superiority

TABLE III DRUGS USED IN SLE

Drug	Dose	Clinical use
Prednisolone	Upto 2 mg/kg/day	Rapid control of moderate to severe disease; Lower dose (0.125-0.5 mg per day) for minor manifestations (arthritis,serositis, cutaneous manifestations)
Intravenous methylprednisolone	10-30 mg per dose for 3 days	Rapid control of severe disease such as neuropsychiatric, renal, hematological, etc
Azathioprine	0.5-2.5 mg/kg/day	Vasculitis, glomerulonephritis, neuropsychiatric PSLE, hematological, steroid sparing
Cyclophosphamide Oral/Intravenous	0.5-2.5 mg/kg/day 500-1000 mg per m^2	Life or organ threatening manifestation, especially nephritis, neuropsychiatric SLE
Mycophenolate mofetil	1200 mg m^2, upto 2000 mg daily in two divided doses	Nephritis, steroid sparing
Hydroxychloroquine	3-5 mg/kg/day, upto 400 mg daily	Skin, arthritis, constitutional; prevents long term flares; favorable effect on lipid profile
Methotrexate	10-15 mg per m^2 per week	Arthritis
Intravenous immunoglobulin	2 g per kg per dose – repeat only at monthly intervals if required	Severe hematological disease

endpoints [51]. However, it has been found to be effective in patients with refractory nephritis, hematological disease and alveolar haemorrhage [52,53]. There are no randomized controlled trials on the use of this drug in pediatric SLE. However, it may be tried in severe refractory disease. Recently belimumab, a B-lymphocyte stimulator (BLyS) inhibitor has been FDA approved in combination with standard therapies for the treatment of active SLE in adults. There are however no studies yet on its effectiveness in pediatric SLE.

Adjunctive Therapy

Photo-protection is encouraged for all patients. Protective clothing, avoidance of sunlight, especially between 10:00 AM till 4:00 PM, and application of adequate sunscreen with SPF of at least 15, on all exposed parts of the body, with re-application if continued exposure after 30 minutes in sunlight is advised. For those on long term corticosteroids, calcium and vitamin D are indicated to prevent bone loss. Antihypertensives are considered for selected patients. It is also important to ensure appropriate nutrition and physical activity.

OUTCOME AND PROGNOSIS

The overall prognosis of jSLE has markedly improved over the past few decades. 10 year survival rates are now >90%, which is comparable with that of adults [54,55]. The major causes of death include renal disease, severe disease flares and infections [54,56,57].

Attention must also be paid to the side effects of medications, especially delayed puberty, growth retardation, osteoporosis, malignancies, infertility and increased risk of infection, which can cause significant morbidity and adversely affect children with this disease. The cost of caring for a child with juvenile SLE was found to range from $146- $650 million annually [58]. Cost is approximately three times higher than for an adult [59].

Pregnancy and juvenile SLE

Studies in adults show that active disease at the time

of conception is associated with poor fetal outcomes [60]. A period of at least 6 months of inactive disease is required prior to conception [60]. Hence pregnancy must be carefully planned. Exposure to drugs like cyclophosphamide or methotrexate are also associated with poor foetal outcomes [61]. In adults with SLE, reported rates of pregnancy loss are about 15-30% [62]. Such data are scarce in juvinle SLE. Silva, *et al.* [63] and co studied females with juvinle SLE for pregnancy outcome and found that the rates of pregnancy loss are similar to that in adults. They found cyclophosphamide use to be related with adverse fetal outcomes, although these patients had more active disease prior to conception and active proliferative glomerulonephritis. Hence it is extremely important to counsel these young women about the importance of a planned pregnancy and the need and access to adequate contraception. Corticosteroids, hydroxychloroquine and azathioprine can be taken safely during pregnancy, with minimal risk to the fetus. However, cyclophosphamide use is contraindicated and its use should be restricted only to life or organ threatening manifestations, with urgent delivery of the fetus [61]. Use of mycophenolate mofetil is also contraindicated. Thus contraception and pregnancy issues should be addressed with all female adolescents with lupus.

CONCLUSIONS

Juvenile SLE is a challenging disease, both to diagnose and treat. It is a more severe disease, as compared to adult SLE, having significantly more renal and CNS involvement. There has been progress in its treatment, with overall improved survival rates. The long term psychological impact of having a lifelong illness, along with the significant side effects of therapy need to be addressed, in order to have a smooth transition through adolescence into adulthood.

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