Clinical and immunological profile of systemic lupus erythematosus in a pediatric population in North India

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Context
Systemic lupus erythematosus is usually missed in the pediatric population because of lower awareness among pediatricians.
Aims
The aim of this work was to study the clinical and immunological profile of lupus in children.
Settings and design
This study was carried out at a tertiary teaching institute of North India; this was a retrospective hospital-based study.
Participants and methods
Case records of 16 children of systemic lupus erythematosus in the age group 5–15 years were reviewed from hospital records.
Statistical analysis used
Means, proportions, and percentages were calculated using Epi Info 7.
Results
The mean age of children at the time of diagnosis was 12.1 years, with a female to male ratio of 5: 1. Fever (81.2%), rash (68.7%), arthritis (56.2%), and photosensitivity (56.2%) were the common clinical manifestations. Anemia was observed in 56.2%, whereas thrombocytopenia was noted in 31.2%. The kidney was the second most common system to be involved, with involvement in 43.7% of cases. Central nervous system involvement was observed in 31.2% of cases. Cardiac involvement was noted in 18% of cases. Antinuclear antibody was positive in all children. Three children died; two died of severe sepsis and one because of cardiogenic shock.
Conclusion
Systemic lupus should be considered a possible cause in adolescents presenting with multisystem involvement.

Keywords:
autoantibodies, children, malar rash, systemic lupus erythematosus, vasculities

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Introduction

Systemic lupus erythematosus (SLE), a rheumatic disease of unknown cause, is characterized by autoantibodies directed against self-antigens, leading to inflammatory damage of many target organs including the joints, kidneys, blood-forming cells, and the central nervous system (CNS). The incidence of lupus is not known, but varies by location and ethnicity. Disease onset before 8 years of age is unusual, although lupus has been diagnosed even in the first year of life. Female predominance varies from 4: 1 before puberty to 8: 1 afterwards [1]. Juvenile SLE is a more aggressive disease than adult SLE, having a markedly higher prevalence and severity of nephritis and CNS disease, requiring higher doses of corticosteroids and other immunosuppressive drugs [2–6].

Participants and methods

We reviewed the hospital records of children younger than 15 years of age who were diagnosed to have SLE at this center between January 2010 and December 2013. The diagnosis of SLE was made on the basis of the American College of Rheumatology criteria [7]. We recorded the details of clinical signs, symptoms, drug intake, and the various investigations performed such as complete hemogram, reticulocytes count, direct Coombs test, liver and kidney function tests, 24-h urinary proteins, and urinary microscopy; relevant radiological investigations were performed where indicated. ECG and echocardiography were also performed when indicated. In the immunological tests, antinuclear antibodies (ANAs) and antibodies titers to double-stranded DNA (dsDNA) were measured using an indirect immunofluorescence test; ANA titer of more than 1: 40 and an anti-dsDNA antibody level of more than 55 IU/ml were considered positive. Estimation of anti-Smith antibodies (anti-SM) was carried out by an enzyme immunoassay and a level more than 80 IU/ml was considered positive. C3 estimation was performed in patients with lupus nephritis. Lupus nephritis was diagnosed by renal biopsy and the biopsy specimen

was examined by light and immunofluorescence microscopy and classified according to the revised WHO criteria [8].

Results

Of 16 children with SLE, three were boys and the rest were females, and the female to male ratio was 5: 1. The mean age at the time of diagnosis was 12.1 years (range 7–15 years). Three of the 16 (19%) children were younger than 10 years of age. Most of the children were diagnosed within 6 months of the initial symptoms. Important clinical features and laboratory parameters are summarized in Tables 1 and 2.

Fever was the most common clinical features observed in 81% of the cases, followed by malar rash (Fig. 1), and arthritis was present in 68 and 56.2% of the cases, respectively. Other features were oral ulcer (43.7%), photosensitivity (56.2%), breathlessness (43.7%), vasculities (37.5%) (Fig. 2), edema (43.5%), and hypertension (31.2%) as shown in Table 1. Neurological manifestations were observed in five (31.2%) patients, seizures were observed in three children, and hemiparesis with upper motor neuron-type seventh cranial nerve palsy was observed in one child. Psychosis was noted in one patient. In the cardiovascular system, pericardial effusion was noted in two children and one child had cardiogenic shock. Malar rash was noted in 68.7% of the patients and was the most common mucocutaneous manifestation, followed by oral ulcer in 43.7%, vasculitic lesions in 37.5% of the cases, and one patient with oral candidiasis. Renal involvement was present in 50% (8/16) of patients. Nephrotic range proteinuria (>40 mg/m^2/h) was found in five patients and microscopic hematuria (>5 RBC/HPF) was observed in seven patients. Azotemia was observed in four patients and two patients required dialysis. Seven patients had lupus nephritis, of whom two had class 2 nephritis, two had class 3 nephritis, and three had class

Table 1 Clinical features

Sign and symptoms	*n* = 16 [*n* (%)]
Fever	13 (81.2)
Malar rash	11 (68.7)
Arthritis	9 (56.2)
Chest pain	2 (12.5)
Breathlessness	7 (43.7)
Oral ulcer	7 (43.7)
Photosensitivity	9 (56.2)
Vasculitis	6 (37.5)
Alopecia	4 (25.0)
Pedal edema	7 (43.5)
Lymphadenopathy	5 (31.2)
Myalgia	6 (37.5)
Ascites	4 (25.0)
Hepatitis	2 (12.5)
Hepatosplenomegaly	6 (37.5)
Serositis	4 (25.0)
Hypertension	5 (31.2)
CNS	5 (31.2)
CVS	3 (18.0)

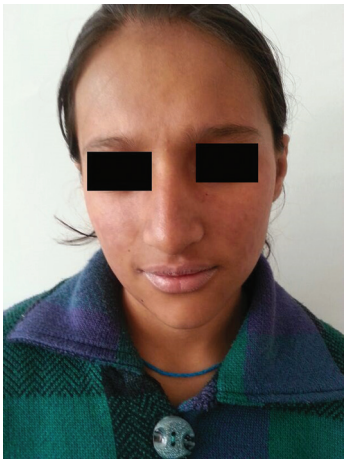
CNS, central nervous system; CVS, cardiovascular system.

Table 2 Laboratory parameters

Investigations	*n* = 16 [*n* (%)]
Hemoglobin (<10 g/dl)	9 (56.2)
Leukopenia (<4000/mm^3)	2 (12.5)
Thrombocytopenia (<100 000/mm^3)	5 (31.2)
Elevated ESR (>20 mm)	11 (68.7)
Serum albumin (<2.5 g/dl)	4 (25.0)
Renal azotemia	4 (25.0)
Hematuria	7 (43.7)
Proteinuria	8 (50.0)
Lupus nephritis	7 (43.7)
Antinuclear antibody positive	16 (100)
Anti-dsDNA antibody positive	9 (56.2)
Low C3 complement	7 (43.7)

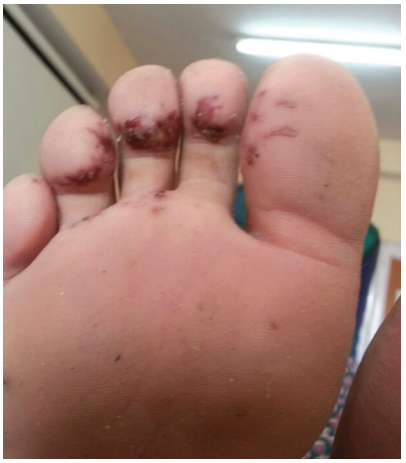
ESR, erythrocyte sedimentation rate.

Figure 1



Malar rash.

Figure 2



Vasculitic lesion in the foot.

4 nephritis according to the WHO classification of lupus nephritis. Hepatosplenomegaly and ascites were observed in 37.5 and 25%, respectively, hepatitis was observed in two patients, and other causes of hepatitis were ruled out. In hematological system, anemia was noted in 56.2%, followed by thrombocytopenia (31.2%) and leukopenia (12.5%). High erythrocyte sedimentation rate was noted in 68.7%. ANA was positive in all cases, antibodies to dsDNA were positive in nine patients, and anti-SM was positive in two cases. Low C3 levels were noted in seven patients. There were three deaths in our series. Two children died of severe septicemia with multisystem involvement and one died because of cardiogenic shock. The rest of the patients are under regular follow-up. We treated our patients with oral prednisolone at a dose of 1–2 mg/kg/day and hydroxychloroquine 3–5 mg/kg/day; these drugs were slowly tapered down after assessing the disease activity and serological remission. Children with lupus nephritis were treated with intravenous methylprednisolone (10–30 mg/kg/dose) for 3 days, followed by oral prednisolone and oral/intravenous cyclophosphamide (0.5–2.5 mg/kg/day). Intravenous cyclophosphamide was administered to the patients who had more severe renal involvement.

Discussion

We diagnosed 16 cases of SLE over the past 4 years. Most of our patients were diagnosed within 6 months of their initial symptoms and the mean age at the time of diagnosis was 12.1 years. In our case series, the female to male ratio was 5 : 1, which is similar to other studies [9,10]. Fever, rash, arthritis, and oral ulcer were the most predominant clinical features, which are also mentioned in other studies [11,12]. In our case series, 43% had breathlessness, which is not mentioned in other studies [10–12]; four out of seven patients with breathlessness had restrictive lung disease on spirometry, and the reasons for breathlessness in the other two cases were anemia and pleural effusion, respectively. Other clinical features reported were alopecia (25%), hepatitis (12.5%), pedal edema (43%), and hypertension (31.2%), identical to that reported by Hari *et al.* [12]. CNS involvement was noted in 31.2% of the patients, which is the same as reported by others [10], and in our series, one patient had complete hemiparesis of the left side of the body because of vasculitis. MRI brain and magnetic resonance angiography showed infarct in striate branches of the right middle cerebral artery. Cardiovascular manifestations are known to occur in up to 30% of children with SLE [13,14]. In our case series, cardiac involvement was noted in 18%; we noted pericardial effusion and cardiogenic shock that was secondary to myocarditis, but we did not find any vegetations or pulmonary hypertension on echocardiography. One child had cardiogenic shock, which was managed with ionotropes, ionodilators, and ventilatory support, but the child succumbed to the illness. Hematological involvement may be noted in up to 50% of children with SLE [13,14]. We recorded hematological involvement in 56% of the patients, which is similar to other studies [12]. Anemia was noted in 56%; three children had severe anemia and required packed red blood cell transfusions, whereas the rest were managed on steroids and showed improvement. Thrombocytopenia was noted in 31% and leukopenia in 12%.

Renal involvement occurs in 30–70% of children with SLE [1]. The most common initial manifestations of nephritis are microscopic hematuria (79%), followed by proteinuria, including nephritic syndrome (55%), and acute renal failure as a presenting manifestation of nephritis is rare (1.4%) [15]. We had two patients with acute renal failure who required dialysis. Renal involvement was noted in 43.7%, which is similar to other studies [9]. Microscopic hematuria and proteinuria were noted in 43 and 50%, respectively. Three of our patients had class 4 nephritis and were managed by monthly intravenous infusions of cyclophosphamide (500–1000 mg/m^2), followed by dosing every 3 months for 18 months. One patient died of severe sepsis with multiorgan dysfunction.

On immunological investigations, ANA positivity was noted in all our patients. Anti-dsDNA antibody titers were positive in 56% of the cases, which is similar to other studies [12]. Anti-SM were tested in only three patients, of whom, two had a positive result. Anti-SM are highly specific for SLE, but these are detected in only about 50% of patients with SLE [6]. Serum complement levels can be a useful measure of disease activity and low levels are observed in about 90% children with active nephritis, and the level increases with treatment [16]. Low complement levels were noted in 43.7%, which were less than that reported in other studies [10,11,17]. As complement is an acute-phase reactant, hypocomplementemia may not be always observed in the acute phase of the disease [13].

Conclusion

We would like to emphasize the fact that the SLE is a multisystem disease that has a varied presentation. In the early phase of the illness, clinical features are often subtle and the diagnosis can be missed if a high index of suspicion is not kept. The disease has an overall poor prognosis; thus, early identification is imperative to a good outcome.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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