Original Articles

CLINICAL AND IMMUNOLOGICAL PROFILE OF SLE: SOME UNUSUAL FEATURES

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Objective: *To study the clinical and immunological profile of children with systemic lupus erythematosus (SLE). Design: Retrospective hospital based study.* ***Setting:*** *Tertiary level center of North India. Subjects: Sixteen children in the age group 4-12 years.* ***Methods:*** *Medical records of children with SLE were analyzed. Clinico pathological features were compared with 2 other series from India. Results: Mean age of children at the time of diagnosis was 10 yr and 8 (50%) children were less than 10 yr of age. The female to male ratio was 7:1. Fever (56.2%), rash (87%) and arthritis (87%) were the common clinical manifestations. Renal involvement was noted in 56.2% of cases. Other clinical features included hemolytic anemia (31.2%), thromobocytopenia (18.6%) and Raynaud's phenomenon (12.5%). Cardiac involvement in the form of severe myocarditis and endocarditis occurred in one patient each. Pulmonary hypertension was the presenting feature in one child with right heart failure. One child had multiple sclerosis along with SLE-a rare combination. ANA positivity was seen in all children. Five children died; two had severe cardiac involvement. Three children had renal involvement and one died of pulmonary hypertension. Two-thirds of subjects with renal involvement improved after therapy according to N1H, Bethesda protocol.* ***Conclusions:*** *SLE must be considered in any child with multisystem disease, as the disease may have certain unusual presentations.*

Key words: *Multiple sclerosis, Pulmonary hypertension, Systemic lupus erythematosus,*

SYSTEMIC lupus erythematosus (SLE) is an immunological disorder with multisystem involvement. Childhood and prepubertal onset occurs in less than 20% of all cases and is characterized by more severe and acute illness(1,2). Though the disease is widely described in adolescents and adults(3,4), the literature pertaining to childhood SLE in India is limited(5,6). As the disease can have protean clinical manifestations, the diagnosis may often be missed if the index of suspicion is not high. We report here the clinical and immunological profile of 16 children of SLE with onset below 12 years of age.

Subjects and Methods

Fourteen children were diagnosed to have SLE out of 380 patients (3.6%) registered at the Pediatric Rheumatology Clinic

(PRC) at our institution, over the last 5 years. Two children were drawn from the Pediatric Hematology Clinic. All children were below 12 years of age at the time of diagnosis.

A detailed clinical history was available in all cases including that of any drug intake likely to cause or exacerbate SLE. Details of clinical examination including serial blood pressure estimations and relevant laboratory investigations (including hematological, biochemical, and immunological parameters) were noted from records in all cases. All patients had complete hemogram with reticulocyte count, renal function tests, urine analysis, liver function test and Mantoux test. Among the immunological tests, lupus erythematosus (LE) cell phenomenon, antinuclear antibody (ANA) and rheumatoid factor (RF) tests were performed in all the cases. Antibody titers to double stranded DNA (dsDNA), Venereal Disease Research Laboratory (VDRL) test and C3 level estimation was performed in 11, 7 and 12 patients, respectively. Patients were subjected to radiological investigations including X-rays of chest, joints and CT scan when indicated. ECG, CSF examination, pulmonary function tests, EEG and cardiac catheterization were done in selected cases. Renal biopsies were done in 9 cases. Of the five patients who died, a complete autopsy was done in one case.

Results

All the 16 children fulfilled the modified ARA criteria for diagnosis of SLE(7). None of our patients was taking drugs known to be associated with ANA positivity. The mean age at the time of diagnosis was 10 years (range 4 to 12 years). Eight of the 16 children (50%) were aged below 10 years. The female to male ratio was 7:1 (14 girls, 2 boys). The mean duration of illness before diagnosis was 1.07 year (range 1 month to 4.0 years). About two-thirds of our patients (10/16) were diagnosed within a year of the initial onset of symptoms.

Fever, rash and arthritis were the common presenting features each seen in 56%, 50% and 50% of the children, respectively. Other common presenting manifestations included renal, neuropsychiatric and hematological. These have been tabulated in comparison with two other recent series on childhood SLE from India *(Table I)*. *Table II* shows the cumulative manifestations of SLE seen in our patients.

Mucocutaneous involvement was observed in 13 (81%) of our cases. Three children presented with an atypical diffuse skin rash. One child had prominent maculopapular rashes which on healing left behind hyperpigmented patches - these lesions were possibly the subacute cutaneous lupus variant of SLE. Skin biopsy in these two cases revealed a classical lupus band of IgG at the dermo-epidermal junction, while the third child showed evidence of small vessel vasculitis. Five pateints had recurrent and painless oral ulcers. One child in addition had mucocutaneous candidiasis. Patchy or diffuse alopecia was noted in 3 patients. Other unusual findings included Raynaud's phenomenon (2 patients) and vasculitic lesions and petechiae of finger tips (1 patient). Arthritis, mild and non deforming, was noted in 9 (56%) cases.

Renal involvement occurred in 56% (9/16) of patients. Nephrotic range proteinuria (>40 mg/sq m/h) occurred in 8 patients, miscroscopic hematuria (>10 RBC/HPF) occurred in 4 and casturia in 2 patients. Azotemia developed in 44.4% (4/9) and in one patient it required peritoneal dialysis. Renal biopsy was done in all the 9 patients. Specimens were evaluated as per the WHO classification for lupus nephritis after histopatho-logical and immunofluorescent staining. Electron microscopy findings

TABLE I - *Clinical Profile at Presentation*

Clinical Feature	Present (n=16)	Chandrashekaran *et al.* (n=59)	Ali *et al.*(5) (n=20)
• Mean age (Years)	8.37	-	9.37
• Children <5 Years	2 (12.5%)	0	1 (5%)
• Female: Male	7:1	4.9:1	2.3:1
• Diagnosis within year of onset	66.6%	—	-
• Nephrotic syndrome	31.25	16.9	25
• Fever	56	67	16
• Rash	50	59	5*
• Arthritis	50	61	60**
• Photosensitivity	43.7	10.1	5*
• Hemolysis	31	0	—
• Neuropsychiatric	31.25	0	5
• Lymphadenopathy	18.7	27.1	—
• Oral ulcers	25	13.5	—
• Cardiac	18.7	1.6	—
• Thrombocytopenia	18.7	—	—
• Pleuropulmonary	12.5	—	—
• Raynaud's	12.5	0	—
• Alopecia	12.5	11.8	

Figures are in percentages
* Represents cutaneous manifestations; ** Represents fever+arthritis.

were available in the patient who was autopsied. It showed discrete to large copious mesangial and subendothelial electron deposits and classical finger print pattern. *Table III* depicts the distribution of renal lesions in our patients. Hypertension was noted in 5 patients and all of them had significant renal involvement. One child had hyper-tensive encephalopathy during the course of illness.

Hemolytic anemia was present in 31.2% of our cases. In 3 subjects it was the presenting feature and 2 of these had very severe hemolysis. The latter had a hemoglobin concentration of less than 6 g/dl; reticulocyte count between 4-40%, and peripheral blood smear showing fragmented cells and polychromasia. Direct Coomb's test was positive in two children. Thrombocytopenia was detected in 3 children and leucopenia in one.

Cardiovascular involvement was seen in the form of pericarditis, myocarditis, endocarditis and right heart failure. One child with severe myocarditis developed refractory hypotension due to cardiogenic shock. Echocardiography showed global hypokinesia with regurgitation across mitral and tricuspid valves. This child died despite maximal imunosupprression (prednisolone and intravenous cyclophosphamide). Autopsy confirmed the presence of myocarditis. Another child, clinically with normal cardiovascular examination,

TABLE ll - *Cumulative Manifestations*

Clinical Feature	Present (n=16)	Chandrashekaran *et al.* (n=59)	Ali *el al.(5)* (n=20)
• Renal	56.2	49.1	75
• Rash	87	69.4	60
• Photosensitivity	87	20.3	20
• Fever	56.2	79.8	60
• Hypertension	31.2	-	-
• Arthritis	49.9	86.6	60
• Neuropsychiatric	43.6	27.1	45
• Hepatosplenomegaly	43.6	39.9	35
• Oral ulcers	43.6	37.2	10
• Hemolytic Anemia	31.2	-	75*
• Thrombocytopenia	18.6	—	10
• Cardiac	18.6	10.2	30
• Pleuropulmonary	12.4	22	20
• Raynaud's	12.5	0	10
• Alopecia	12.5	49	29
• Leucopenia	6.1	18.4	0

Figures are in percentages
*Indicates anemia; hemolytic or otherwise

TABLE III---*Distribution of Renal Lesions According to WHO Classification of Lupus Nephritis*

Histopathology	WHO Class	No. of patients (n=9)	Outcome
• Normal	Class I	0	
• Mesangial	Class II	1 (11.1)	Improved
• Focal segmental proliferative	Class III	2 (22.2)	Improved
• Diffuse proliferative	Class IV	4 (44.4)	2 died; 2 improved
• Membranous	Class V	1 (11.1)	Improved
• Glomerular sclerosis	Class VI	0	
• Tubulo-interstitial	1 (11.1)	Died	

Parentheses indicate percentages.
*Treatment according to NIH, Bethesda protocol (8).

incidentally had a large pedunculated vegetation on mitral valve without any valvular compromise. He died following sudden pulmonary hemorrhage. One child had right heart failure secondary to pulmonary hypertension as demonstrated on cardiac catheterization.

Four children (25%) had neuropsychiatric manifestations as presenting corn-plaints. Seizures were seen in 43.2% (7/16)

and psychosis or behavioral disturbances in 31.2% (5/16). EEG (done in four cases) was normal in two, while in one each had findings suggestive of generalized seizure and focal seizure with secondary generalization. CT scan was done in five patients and was essentially normal except in one patient where it showed a ring lesion. One child had choreoathetoid movements of the right half of the body at presentation. One child had multiple sclerosis associated with SLE. She had presented with urinary retention, quadriparesis and optic neuritis as three different episodes before developing the other features suggestive of SLE. Investigations revealed oligoclonal bands in CSF and abnormal auditory and visual evoked potentials.

ANA was positive in all the cases *(Table IV)*. LE cell could be demonstrated in only 4 children. Antibodies to dsDNA were done in only 11 patients and titers were significantly high in 8 of them. A biologically false positive VDRL was noted in 2 out of 7 cases where it was done. Lupus anticoagulant was detectable in 2 of the 4 cases where this investigation was performed. Serum C3 levels were low in 58.3% (7/12) of our cases. AntiSm antibody was not tested in any child.

There were five deaths (31.2%) in our series. Two of these resulted from severe multisystem involvement including cardiovascular complications (myocarditis and endocarditis). One child with multiple sclerosis died at home, while another succumbed to an infective illness at another hospital. One girl with severe pulmonary hypertension has not come for follow-up and is presumably dead considering the advanced stage of her illness.

Rest of the patients have been followed up for periods ranging between 6 to 60 months (mean = 2.4 yrs). Most of our patients with renal involvement (75%) have shown significant improvement. Hypertension is well under control and renal functions are preserved in majority of the cases. We treated our children with 1-2 mg/kg/day of prednisolone and after complete suppression of the disease gradual tapering was done. Children with lupus nephritis were treated according to NIH, Bethesda protocol with prednisolone and intravenous cyclophosphamide(8).

In addition to these 16 patients, there were 7 children (2 girls and 5 boys) who had isolated renal involvement with atypical nephrotic syndrome and ANA positivity. We did not include these patients in our series, as they did not fulfill the requisite criteria for the diagnosis of SLE(7).

TABLE IV- *Immunological Findings*

Features	Present (n=16)	Chandrashekaran *et al.* (n=59)	*Ali et al.(5)* (n=20)
• LE cell	25.0(4/16)	50.0	60
• Anti ds DNA	72.7(8/11)	84.6	87.5
• ANA	100(16/16)	92.3	100
• VDRL	28.5(2/7)	3.3	—
• Low C3	58.3(7/12)	57.7	75
• Rh Factor	—	3.3	—

Figures are in percentages.
*Parentheses indicate positive results in patients in whom the test was performed.

Discussion

With increasing awareness among pediatricians and easy availability of immunological investigations, childhood SLE is now more often and more readily diagnosed even in the first decade of life(5,9). We encountered 16 cases over the last 5 years. Majority (63.5%) of the children were diagnosed within a year of their initial manifestations. The mean duration of illness prior to diagnosis was 1.07 years in our series. The mean age at the time of onset of symptoms is 8.37 years which is lowest among other pediatric series from India suggesting that with more awareness one may diagnose cases even at younger age(5,6,9). There were 2 children below 5 years of age (one being male)-presentation at such a young age has rarely been reported^) in the Indian literature. The female to male ratio in our series is high compared to other series for which we do not have any plausible explanation.

SLE is a multisystem disorder and the manifestations can be very variable. In atypical cases the diagnosis may be missed if the index of suspicion is not high. Such children may sometimes continue receiving inappropriate treatment without a composite diagnosis as exemplified by some of our cases. The child with pulmonary hypertension was initially thought to have primary pulmonary hypertension and it was only later that a diagnosis of SLE could be established. Another child with multiple sclerosis was suspected to have SLE when she developed renal failure and probably had a rare combination of these two uncommon diseases(10). Likewise the children with hemolytic anemia could easily have been missed if appropriate immunological investigations were not sought for.

The most common clinical manifestation after mucocutaneous features was nephrotic syndrome (NS) seen in 56.2% of the cases. Majority of our patients with lupus nephritis had pathological changes consistent with Class III and Class IV lupus nephritis (WHO classification). One child presented with acute anuric renal failure requiring peritoneal dialysis. She had interstitial nephritis with normal glomeruli on histopathology, a rare presentation of SLE(IO). Our series has similar proportion of renal cases as compared to other series from India (6). At our center all the children with nephrotic syndrome get routinely screened for secondary causes. It is our contention that SLE must be ruled out as a cause of NS in children especially in those with atypical features such as hypertension, hematuria or deranged renal functions. Some patients of SLE may present predominantly as nephrotic syndrome with vague or transient extrarenal manifestations. These patients may be erroneously labelled as primary/idiopathic glomerulonephritis unless a diligent search is made for serological markers(ll). ANA should be done before starting steroids, so as to avoid false negative results. Such a dilemma is well highlighted in 7 if our cases, as mentioned earlier. Though these patients did not fulfill the criteria for SLE, it is possible that the other manifestations have been suppressed by the concommitant administration of steroids for nephrotic syndrome. Only long term follow up will resolve the issue. However, such patients can be labelled as having "possible SLE"(2).

Hematological manifestations may be seen in upto 50% of children with SLE(1,2). We recorded hematological involvement in 31% of the cases. In 3 of these cases, it was the presenting manifestation. Hemolytic anemia in SLE is often difficult to treat and may not respond to therapy with prednisolone. Of the two patients who did not respond well to steroids subsequently,

one was given a trial of IVIG, while the other was put on long term azathioprine. None of these therapeutic modalities proved to be of any added benefit. It is of interest that in both of them the disease process so far has neither overtly involved any other organ system nor was there a depression of any other cell line. Continuing hemolysis seems to be the only management problem. Splenectomy, recommended for the treatment of such a hemolytic anemia (due to SLE) which does not respond to an adequate trial of immunosuppressive drugs(12), proved to be of transient benefit in one child but she relapsed again after remaining well for 3 months.

Cardiovascular (CVS) manifestations involving pericardium, myocardium and endocardium are known to occur in upto 30% of children with SLE(1,2). We observed CVS involvement in 18.6% cases. It is interesting to note that three children who died in our series had significant CVS disease. While myocarditis (proven on autopsy) with refractory hypotension was the predominant manifestation in one(13), echocardiography revealed a large (1 cm x 0.7 cm) pedunculated vegetation of the mitral valve in the other child. Though large size of the vegetation favors a diagnosis of infective endocarditis, in the absence of autopsy findings, underlying verrucous endocarditis with smaller lesions (1-4 mm) with or without superimposed infection cannot be ruled out (1,2,14,15). Pulmonary hypertension as the isolated presenting manifestation of SLE is extremely rare. It may result from vasculitis, thromboembolism or interstitial lung disease(16,17). However, in presence of lupus anticoagulant and reactive VDRL in this child it seems to be the manifestation of antiphospholipid antibody syndrome(18).

The incidence of neuropsychiatric manifestations (43.2%) seen by us is higher than that reported by others(5,6). Moreover, besides seizures and psychosis which have been frequently reported in SLE, one of our patients had choreoathetoid movements without any other neurodeficit. Cranial CT scan in this child was normal. Lupus anticoagulant test was, however, positive. Choreoathetoid movements are an extremely uncommon CNS manifestation of lupus(l,2,19). One girl with multiple sclerosis and SLE probably was the first such case in the pediatric age group(10).

ANA positivity was seen in all our patients. Anti dsDNA antibody titers were positive in 8 (72.2%) of the cases. Though lower than other pediatric series(5,6), it is in concordance with the figures reported by Tan *et al.{7).* In some patients dsDNA titers could be done only after the steroids had already been administered for sometime. Hypocomplementemia, noted in 58% of our cases was again less commonly seen than in other two series from India(5,6). As complement is an acute phase reactant, hypocomplementemia may not be always seen in the acute phase of the disease(l).

To conclude, our series again highlights the fact that SLE can present with protean clinical manifestations. The primary diagnosis can often be missed if the index of suspicion is not high, specially so in children where the overt clinical features *(e.g.,* butterfly rash) of the disease may not be very prominent. The disease may have certain uncommon and unique ways of presentation which may mislead the pediatrician. One should suspect SLE even if classical criteria are not fulfilled and follow such patients closely. Childhood SLE has an overall poor prognosis. Though the follow-up of this study is limited, yet it emerges that children with SLE having

renal or cadiovascular complications have worse prognosis.

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