Spectrum of Pediatric Systemic Lupus Erythematosus at Queen Rania Al-Abdullah Hospital for Children

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ABSTRACT

Objectives: The aim of this study is to describe clinical signs, symptoms, laboratory characteristics, and medication used in pediatric Systemic lupus Erythematosus, both at presentation and during the course of the disease in Jordanian children at Queen Rania Al-Abdulla Hospital for children.

Methods: This is a retrospective descriptive study that included patients managed over a period of 11 years, from January 2000 to December 2010. The charts of 25 patients from the pediatric Rheumatology unit at Queen Rania Al-Abdulla Hospital for children, who met four or more of the revised American College of Rheumatology classification criteria for Systemic lupus Erythematosus were reviewed.

Results: There were 22 females and three males with F: M ratio of 7.3:1. The mean age at diagnosis was 10.9 years (range 7-14 years) with only five patients (20%) below the age of 10 years. The mean time from the start of illness to diagnosis was 8.6 month (range 1-36 months). At presentation cutaneous manifestations were found in 17 (68%) patients, 60% of patients had arthritis. Serositis and neurological manifestations were seen in 24% of cases. Hematological dysfunctions were present in 48%. Renal involvement was found in 40% of cases. Kidney biopsy was done for seven patients with renal manifestations. Three had class IV, two class III and two class I World Health Organization nephritis stage classification. No organ damage was found in 18 patients with Systemic lupus Erythematosus, while three patients developed end stage renal disease, two had neuropsychiatric disease (one cerebrovascular accident and one with chorea), one had cataract and one had peripheral vascular thrombosis, and gangrene of the hands and feet. Antinuclear Antibodies was positive in all patients.

Conclusion: To the best of our knowledge this is the first review of Systemic lupus Erythematosus in pediatric population in Jordan. Comparison of our cohort with other reports from our region and other parts of the world confirmed that more or less the pediatric Systemic lupus Erythematosus behavior in presentation and laboratory findings is comparable.

Key words: Describe, Systemic lupus Erythematosus

JRMS December 2014; 21(4): 12-18 / DOI: 10.12816/0008060

Introduction

Systemic lupus Erythematosus (SLE) is a multisystem, inflammatory, autoimmune disease that affects both children and adults, with approximately 20% of cases starting in childhood. It is rarely seen in children below the age of five years and most pediatric patients are diagnosed in adolescence.[1] The female to male ratio is variable with age, rising from 4:3 in the

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Manuscript received September 10, 2012. Accepted February 7, 2013

first decade to 4:1 in the adolescence.[2] The etiology of SLE remains unknown; however, complex interplay between genetic and environmental factors appears to contribute to its immunopathogenesis.[3] Its immunopathogenic hallmark is polyclonal B-cell activation, leads to hyperglobulinemia, autoantibody production, and immune complex formation; this in turn leads to inflammation and damage that can affect multiple organ system.[4] The disease has variable presentation including constitutional symptoms, serositis, arthritis, and cutaneous, renal, hematological, cardiac, pulmonary and neurological manifestations. Atypical picture is seen as well. The course of SLE is characterized by periods of flare and remission.[5] Children with childhood-onset SLE have more active disease at presentation and over time than do adults with SLE, especially active renal disease.[6] Managing childhood and adolescent SLE patients with or without Lupus Nephritis is both interesting and challenging; optimally this should be within a multi-disciplinary team of health professionals; as a result of the shortage of clinical trials, treatment protocols vary between different centers.[7]

The aim of this study is to describe clinical signs, symptoms, laboratory characteristics, and medication used in pediatric SLE, both at presentation and during the course of the disease in Jordanian children at Queen Rania Al-Abdulla Hospital for children (QRAHC).

Methods

This is a retrospective descriptive study that included patient managed over a period of 11 years, from January 2000 to December 2010. The charts of 25 patients from the Pediatric Rheumatology Unit at QRAHC who met four or more of the revised American College of Rheumatology (ACR) classification criteria for SLE were reviewed., according to these classification criteria patient is considered to have SLE if at least four criteria are cumulatively fulfilled, with a high sensitivity and specificity (both 96%) in patients with an already established diagnosis.[8]

The onset of diagnosis had to be at 14 years of age or under as per hospital protocol. All patients' charts were reviewed for demographic, characteristics, clinical and laboratory findings. Revision for all charts was done from the disease onset till the present time for the following parameters: Gender, age at diagnosis, initial manifestation, initial laboratory findings, disease duration, in addition to the disease progression. Disease activity was determined using the Systemic lupus Erythematosus Disease Activity Index (SLEDAI) which is an easy assessment tool to use. Twenty-four features that are attributed to lupus are listed, with a weighted score given to any one that is present, the more serious manifestations (such as renal, neurologic, and vasculitis) are weighted more than others The maximum possible score is 105.[9] The clinical features and laboratory abnormalities were defined according to ACR classification criteria for SLE.[8]

Disease damage was evaluated using the definitions of the Systemic Lupus International collaborative Clinics/American College of rheumatology (SLICC/ACR) Damage Index (SDI).[5]

Results

The total number of SLE patients diagnosed in the period between 2000 and 2010 was 25. The demographic characteristics of the patients are summarized in Table I.

Table I: Patient demographic data

Demographic Data	Number (%)
Number of Patient	25
Male	3 (12%)
Female	22 (88%)
Female : Male	7.3:01
Mean Age at Diagnosis	10.9 Years
Mean Time of Diagnosis Delay	8.6
Mean Duration of Follow Up	40 Month (1-75 month)

At presentation cutaneous manifestations were found in 17 (68%) patients as malar rash in 13 (52%), photosensitivity in 14 (56%), discoid lupus in one (4%) and oral ulcers in nine (36%) patient. More than half (60%) of patients had arthritis. Serositis and neurological manifestations were seen in 24% of cases. Hematological dysfunctions were manifested in 48% of our cohort. The most common was leukopenia (24%), anemia (20%) followed by thrombocytopenia (16%), and lymphopenia (16%). The diagnosis of SLE was made as late as three years in one female patient presented with

chronic Idiopathic Thrombocypenic purpura (ITP) who underwent splenectomy. It is worth mentioning that platelets were normal in most of patients at diagnosis. The renal involvement was found in 40% of cases. The most common manifestations were proteinuria (40%) and microscopic hematuria (8%). The frequency of various diagnostic clinical and laboratory manifestation at the time of diagnosis are shown in Table II.

Table II: The frequency of the various diagnostic features of SLE at the time of diagnosis

Clinical Features	Number	%
Cutaneous	17	68
Malar Rash	13	52
Discoid Rash	1	4
Photosensitivity	14	56
Oral Ulcers	9	36
Musculoskeletal	15	60
Arthritis	15	60
Renal	10	40
Proteinuria	10	40
Glomerulonephritis	2	8
Cellular Casts	6	24
Serositis	6	24
Pleuritic Pain	3	12
Pleural Effusion	1	4
Pericarditis	2	8
Neurologic	6	24
Seizures	1	4
Psychosis	4	16
Chorea	1	4
Hematologic Disorder	12	48
Hemolytic Anemia	5	20
Leukopenia	6	24
Lymphopenia	4	16
Thrombocytopenia	4	16
High ESR	21	84
Immunologic	22	88
Ant Ds DNA	22	88
Ant Smith	2	8
Anti-Phospholipid	10	40
Anti Cardiolipin	10	40
Lupus Anticoagulant	4	16
VDRL	Non	0
Coombs Test	13	52
ANA	25	100

Antinuclear Antibodies (ANA) was positive in all patients. It was above 1:640 in 80% of patients. A variety of nonspecific (atypical) non-diagnostic features were observed, as initial manifestation in almost all patients. The most common was fatigue in 21 (87%), anorexia in 18 (75%), alopecia in eight (33 %) (Table III).

Table III: Non-specific (atypical) initial manifestations

Features	Number	%
Fever	7	28
Abdominal Pain	4	16
Weight Loss	6	25
Anorexia	18	72
Fatigue	21	84
Alopecia	8	32
Peripheral Lymphadenitis	4	16
Ocular Involvement	2	8
Autoimmune Hepatitis	2	8
Sicca Syndrome	1	4
Raynaud's Phenomenon	10	40
Vasculitis	8	32
Digital Ulceration	2	8
Cardiac	1	4
Headache	5	20

Kidney biopsy was done for seven patients with renal manifestations. Three had class IV, two class III and two class I WHO) nephritis stage classification.[10] SLE course was assessed using SLEDAI.[9] Assessment was done at initial presentation and at each follow up visits Table IV. This showed significant decrease in SLEDAI at six and 12 months after diagnosis in all patients. SDI score showed no organ damage in 18 patients with SLE (score: 0), while seven patients scored at least I.[5,6] Three patients developed end stage renal disease, two had neuropsychiatric disease (one cerebrovascular accident and one with chorea), one had cataract and one developed peripheral vascular thrombosis, and gangrene of the hands and feet. The clinical and laboratory features of our childhood SLE patients were compared with regional experience (Table V).

All patients (n=25) received corticosteroids for the disease control (oral prednisolone and or pulses of intravenous methyl prednisolone when applicable). The second most commonly used medication was hydroxychloroquine (n=18, 72%). Immunosuppressive medications were used in 22 patients (88%), including Azathioprine (n=12, 48%), Methotrexate (n=10, 40%), Mycophenolate mofetil (n=4, 16%) and Cyclophosphamide (n=9, 32%) in lupus nephritis and neuropsychiatric SLE. Supportive medication, including calcium supplement, vitamin D, gastric protective medication, and antibiotic prophylaxis were given as propriety. Pneumococcal and H influenza vaccine were given to all 25 patients (100%).

Table IV: SLEDAI Score

	At Time of Diagnosis	6 Month Post Diagnosis	12 Month Post Diagnosis
Total	18	3.5	3
Renal Disease	22.5	3.6	2.8
CNS Disease	21	2.5	2.5
Both	26	2.5	3
None	8.4	2	0

Table V: Clinical manifestations in our cohort and other series

Clinical Features	Our Cohort	Oman [15] N=50	Nigeria [23] n=11	Europe [36] N=5	Canada [22] N=25	India [37] N=44	Saudi Arabia [30] N=30
Malar Rash	52%	Cutaneous 70%	27%	69.60%	61%	Cutaneous 54%	47%
Photosensitivity	56%	NA	36%	44.60%	17%	NA	NA
Oral Ulcers	36%	10%	36%	28.60%	21%	20%	3.30%
Arthritis	60%	76%	91%	59.30%	61%	68%	73%
Hematological	48%	68%	100%	63.60%	55%	54%	87%
Neuropsychiatric	24%	18%	36%	25%	16%	25%	30%
Renal	40%	64%	100%	63%	37%	54%	73%
ANA	100%	100%	NA	NA	100%	96%	100%
Anti DsDNA	100%	82%	NA	60.70%	72%	70%	90%

Discussion

To the best of our knowledge, this is the first review of SLE in pediatric population in Jordan. This is a retrospective single center study carried out in the division of pediatric rheumatology at QRAHC / King Hussein Medical Center. It is the only referral unit for children with rheumatic disorders in the country.

The current best estimate is that SLE affects between 5,000 and 10,000 children in the United States.[11] In France, the epidemiological survey in pediatric lupus Paris area, reported an incidence of 0.22 cases for 105 children.[12] However, Because our cohort is not necessarily representing all cases of pediatric SLE in the country, we could not comment on the exact prevalence of the disease in our population which needs, a more formal epidemiological survey. Female gender preponderance (F: M=7.3:1) in our cohort is similar to epidemiological study on adult patients, it is comparable to data reported from United Kingdom (7.4:1),[13] and Iran (8:1).[14] It is higher than ratio reported from Oman (5.3:1),[15] Saudi Arabia (5.8:1),[16] and the French multicenter study (4.5:1).[17] The mean age at diagnosis of our patients was 10.9 years, which is consistent with early report from Kuwait (10.7 years).[18] But it is lower than that reported from Saudi Arabia (21.1 years),[19] and Egypt (11.9 years)[20] cohorts. This discrepancy might be explained by enrolment of patients above the age of 14 in both cohorts. Cutaneous manifestations observed in 68% of patients which is consistent with data from Egypt[20] and France.[17] Musculoskeletal manifestation was seen in 60% of patients which is comparable to the clinical features of SLE in this age group, reported by Plachinotta *et al*.[21]

Nonspecific constitutional symptoms were the most common feature at initial presentation: fatigue (87%), anorexia (75%) and fever (28%), which is comparable to the finding of Hiraki *et al*.[22] Renal involvement was found in 40% (n=10) of our patients which is comparable to the Canada (37%),[22] but much less than that from Nigeria (100%)[23] and Oman.[15] In our study, 71% of patients who underwent renal biopsy had severe renal involvement WHO class IV, II three out of seven, and two out of seven respectively, which is similar to the findings of Brunner *et al*.[6] This increased frequency and severity of renal disease in childhood SLE supports the findings of previous studies.[24]

Hematological abnormalities were seen in 48% of patients and is comparable to what was reported from Egypt[20] and less than Saudi Arabia (66.6%), France (72%) and Turkey.[17,19,25] In our cohort, one of the interesting findings was that normal or low platelets with high ESR found in 90% of cases. Neuropsychiatric SLE was found in 24% of cases including seizures, psychosis and, most

commonly, headache with almost the same percentage reported by Benseler *et al*.[26] Cardiac and pulmonary involvement were found in 8% and 12% respectively which correlate with data from Kuwait [18] and Egypt [20] but much less than that reported from Saudi Arabia.[19]

Constitutional symptoms were found in almost all patients persisting for more than three weeks consistent with what reported by Zonana-Nacal *et al*.[27] These symptoms may be due to active inflammation, medicines-related or multifactorial.[28] Thus, SLE should be considered in the differential diagnosis in a child presented with persistent constitutional symptoms and high ESR. ESR was high in all our patients, while the CRP was normal or mildly elevated in most cases which are consistent with the finding reported by Taddio *et al*.[29] The ANA was positive in all patients which is similar to what was reported in the Saudi cohort,[30] but different from what was reported from other studies.[12,17]

The majority (88%) of our patients were positive for anti-ds DNA which was consistent with Bader-Meuner *et al*.[17] and Taddio *et al*. reports.[29] Anti cardiolipin antibodies were positive in 40% of cases that is less than a result of multi-center study by Taddio *et al*.[29] The SLEDAI showed significant decrease after six months from 18 to 3.5 respectively but no further significant decrease after one year of treatment that is consistent with Canadian reports.[22]

Our policy in treating pediatric SLE patients with corticosteroid and various immunosuppressive medications, aiming to prevent organ damage is comparable to what has been used in other countries. In our cohort study corticosteroids were used in all patients and hydroxychloroquine in around three-fourths. Differences have been noticed regarding how frequent immunosuppressant medications have been used. The use of corticosteroids was recommended as initial therapy by Stephen and Kjell in their review of modern therapeutic strategies for pediatric SLE and lupus nephritis,[7] while multiple studies have demonstrated the therapeutic and protective effects of antimalarial medications in SLE.[31,32] We used immunosuppressant medications including azathioprine, methotrexate, mycophenolate mofetil and cyclophosphamide according to the severity of the disease as well as the variability of organ involvement. The use of azathioprine[7] Mycophenolate mofetil,[7,33] Cyclophosphamide[7,34] and Methotrexate[35] in Juvenile SLE has been reported.

Conclusion

According to this retrospective study, pediatric SLE in our population is mostly diagnosed after the age of 10 years with female gender predominance. Persistent nonspecific manifestations such as fatigue and fever accompanied with cutaneous manifestation were the most common presenting diagnostic features followed by musculoskeletal manifestations. Comparison of our cohort with other reports from our region and other parts of the world confirmed that more or less the pediatric SLE behavior in presentation and laboratory findings is comparable with some variation.

We believe that we need more detailed prospective and epidemiological studies to determine the prevalence and incidence of the disease as well as the long term outcome of the disease in our community.

References

1. **Ilowite, Beth S. Gottlieb and Norman T.** Systemic Lupus Erythematosus in children and adolescents. *Pediatr Rev* 2006; 27: 323-330.
2. **Falcini F, Nacci F.** Systemic lupus erythematosus in the young: the importance of a transition clinic. *Lupus* 2007;16: 613-617.
3. **Midgley A, McLaren Z, Moots RJ, *et al*.** The role of neutrophil apoptosis in juvenile onset systemic lupus erythematosus. *Arthritis & Rheumatism* August 2009; 60: 2390–2400.
4. **Vasoo S, Hughes GR.** Theory ,targets and therapy in systemic lupus erythematosus. *Lupus* 2005; 14: 181-188.
5. **Brunner HI, Silverman ED, To T, *et al*.** Risk factors for damage in childhood-onset systemic lupus erythematosus. *Arthritis Rheum* 2002; 46: 436-444.
6. **Brunner HI, Gladman DD , Ibanez D, *et al*.** Difference in disease features between childhood-onset and adult onset systemic lupus erythematosus. *Arthritis Rheum* 2008; 58: 556-562.
7. **Marks SD, Tullus K.** Modern therapeutic strategies for pediatric systemic lupus erythematosus and lupus nephritis. *Acta Pdiatrica* 2010; 99: 967-974.
8. **Hochberg MC,** Updating the American College of Rheumatology revised criteria for

classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.

9. **Gladman DD, Ibanez D, Urowitz MB.** Systemic lupus erythematosus disease activity index 200. *J Rheumatol* 2002; 29: 288-291.
10. **Weening JJ, Agati VD, Schwartz MM, *et al.*** The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 2004; 65: 521-520.
11. **Lehman TJ.** Systemic lupus erythematosus in children and adolescents. In: Hahn B, Wallace DA ed, Dubois' Systemic Lupus Erythematosus. 5th, chepter l. WB Saunders, 1996.
12. **Bader-Meunier B, Quartier P, Deschênes G, *et al.*** Childhood-onset systemic lupus erythematosus. *Arch Pediat* Feb 2003; 10(2): 147-157.
13. **Michielson CF, Bernstein MCR, Hughes GRV, Ansell BM.** Systemic lupus erythematosus in childhood. *Annals of the Rheumatic Diseases* 1981; 40: 325-331.
14. **Moradinejad MH, Zamani GR, Kiani AR, and Esfahani T.** Clinical features of juvenile systemic lupus erythematosus in Iranian children. *Acta Rheumatology Port* 2008; 33: 63-67.
15. **Abdwani RI, Rizvi SG, Nour EL.** Childhood systemic lupus erythematosus in Sultanate of Oman: demographics and clinical analysis. *Lupus* 2008; 17: 683-686.
16. **Al-Mayouf SM, Sonbul AL.** Influence of gender and age of onset on the outcome in children with systemic lupus erythematosus. Clin Rheumatol 2008; 27: 1159-1162.
17. **Bader-Meuner B, Armengand JB, Haddad E, *et al.*** Initial presentation of childhood-onset systemic lupus erythematosus: H French multicenter study. *J Pediatr* 2005; 146: 648-653.
18. **Al Saeid K, Kamal M ,Haider MZ,AL-Enezi HM, Malaviya AN** Systemic lupus erythematosus in Kuwaiti children :organ system involvement and serological findings, Lupus**.** 2004; 13: 613-617.
19. **Bahabri S, Sabban EA, Al-Rashed A, *et al.*** Juvenile systemic lupus erythematosus in 60 Saudi children. *Ann Saudi Med* 1997; 17: 612-615.
20. **Bakr A.** Epidemiology treatment and outcome of childhood systemic erythematosus in Egypt. *Pediatr Nephrol* 2005; 20: 1081-1086.
21. **Plachinotta FR, Schiavo B, Vittadello F, *et al.*** Distinctive clinical features of pediatric systemic lupus erythematosus in three different age classes. *Lupus* 2007; 16: 550-555.
22. **Hiraki LT, Benseler SM, Tyrrell PN, *et al.*** Clinical and laboratory characteristic and long-term outcome of pediatric systemic lupus erythematosus :A longitudinal study. *J Pediatr* 2008; 152: 550-60.
23. **Olowu AW.** Childhood-onset systemic lupus erythematosus. *Journal of the National Medical Association* 2007; 99: N 7.
24. **Cameron JS.** Lupus nephritis in childhood and adolescence. *Pediatr Nephro* 1994; 8: 230-90.
25. **Gokce M, Bilginer Y, Besbas N, *et al.*** Hematological features of pediatric systemic lupus Erythematosus: suggesting management strategies in children. *Lupus* 2012; 21: 878-84.
26. **Benseler ED, Silverman SM.** Neuropsychiatric involvement in pediatric systemic lupus erythematosus. *Lupus* 2007; 16: 564-571.
27. **Zonana-Nacach A, Roseman JM, McCwin Jr G, *et al.*** Systemic lupus erythematosus in three ethnic groups VI: factors associated with fatigue within5 years of criteria diagnosis. LUMIINA study Group. lupus in minority population: Nature Vs Nurture. *Lupus* 2000; 9: 101-109.
28. **Ad HOC** Committee on systemic lupus erythematosus Response criteria for fatigue. Measurement of fatigue in systemic lupus erythematosus: a systemic review. *Arthritis Rheum* 2007; 57: 1348-1357.
29. **Taddio A, Rossetto E, Rose CD, *et al.*** Prognostic impact of atypical presentation in pediatric systemic lupus erythematosus : Results from a multicenter study. *J Pediatr* 2010; 156: 972-7.
30. **Muzaffer MA, Al-Mayouf SM.** Clinical and laboratory variables of childhood systemic lupus erythematosus in western province of Saudi Arabia. *Rheumatol Int* 2011; 31: 23-26.
31. **Kasitanon N, Fine DM, Haas M, et al.** Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. 2006; 15: 366-370.
32. **Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA.** Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2010; 69: 20-28.
33. **Nannini C, Crowson CS, Matteson EL, Moder KG.** Mycophenolate mofetil is effective in reducing disease flares in systemic lupus erythematosus: a retrospective study. *Lupus* 2009; 18: 394-399.
34. **Bertsias GK, Ioannidis JPA, Aringer M, *et al.*** EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis* 2008; 67: 195-205.
35. **Fortin PR, Abrahamowicz M, Ferland D, *et al.*** Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis & Rheumatism* 2008; 59(12): 1796-1804.

36. **Hoffman EA, Lauwerys BR, Keyser FDE, *et al*.** Juvenile onset systemic lupus erythematosus: different clinical and serological pattern compared to adult onset systemic lupus erythematosus. *Ann Rheum Dis* 2009; 68: 412-415.
37. **Mondal R, Nandi M, Ganguli S, *et al*.** Childhood lupus: Experience from Eastern India. *Indian J Pediatr* 2010; 77: 889-91.