Outcome of adult Saudi patients with childhood-onset systemic lupus erythematosus

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Abstract

Objective

We aimed to describe the social, educational, employment and long-term clinical outcomes of adults with childhood-onset systemic lupus erythematosus (SLE) in a Saudi cohort

Methods

All adult patients with childhood-onset SLE who were treated and had regular follow-up between 1990 and 2013 at King Faisal Specialist Hospital and Research Centre (KFSH-RC), Riyadh were included. The long-term outcome measures comprised SLE Disease Activity and Damage Indices at the last follow-up visit and death related to SLE. Social, educational and employment history were obtained via personal or phone interviews.

Results

Forty-eight patients (45 female) were included, whose mean age was 23.6±4 years and mean disease duration 15±4 years. At the last follow-up visit, 24 (50%) patients were found to have active disease with mean of accrual damage index of 2 (0–7). Forty patients (83%) had renal involvement, 7 (15%) of them progressed to end stage renal disease, 5 patients underwent renal transplant, 2 failed the transplant and are currently on haemodialysis. Sixteen patients had central nervous system involvement in the form of seizure disorder (6 patients), chorea (3 patients) and cerebrovascular accident (3 patients). Forty-three patients completed high school and 21 joined a college. Six patients were in employment. Eight patients got married and 5 of them had children. There were 3 deaths related to SLE (6.25%), mainly due to infection.

Conclusion

Our cohort indicates that the outcome of adult Saudi patients with childhood-onset SLE was satisfactory and comparable to earlier reports.

Key words

systemic lupus erythematous, childhood, outcome, disease damage, Saudi Arabia

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease, with a wide range of clinical and laboratory findings, depending upon the type and severity of organ involvement (1). SLE predominantly affects young women in reproductive age. However, of all SLE patients, 20% are diagnosed during childhood (2, 3).

Disease expression influenced by different factors including ethnicity, gender and age at disease onset. Recently verified disease indices from several large cohorts of SLE patients suggest that children usually have more severe disease with higher rates of organ involvement at disease onset. Furthermore, children usually have disease that is more active at presentation and over time than do adults with SLE (4-6). Children have often an aggressive clinical course and more frequent renal involvement as compared to adults. Accordingly, patients who develop SLE in childhood are likely to face a lifetime of complications and accrue more damage related to their disease and treatment (7- 10).

Health outcomes in childhood-onset rheumatic diseases have become an interesting research subject. Several studies published in the last decade have examined the long-term health, functional and quality of life outcomes of adults with childhood-onset rheumatic diseases. The outcome can no longer be considered separately from the results of comprehensive health care (11-13). Although most studies have been in the area of juvenile idiopathic arthritis, there are increasing numbers of studies in childhood-onset SLE. Recent reports have shown a remarkable improvement of the survival and prognosis in childhood-onset SLE, probably due to the implementation of new therapeutic strategies including the early introduction of immunosuppressive drugs (14-16).

As increasing numbers of children with SLE survive into adulthood, understanding the adult outcome of childhood-onset SLE has become increasingly important.

We have the privilege at King Faisal Specialist Hospital and Research Centre, (KFSH-RC), Riyadh to follow a large cohort of children with SLE. Those over 14 years of age are usually transferred to adult rheumatology care to provide ongoing and comprehensive clinical care.

To the best of our knowledge, there is no available published data from the Middle East about the impact of childhood-onset SLE on adult patients.

In this study, we have highlighted the social, educational and long-term clinical outcome of adult Saudi patients with childhood-onset SLE.

Methods

All patients with childhood-onset SLE who were followed at our paediatric SLE clinic and transferred to adult rheumatology clinics at KFSH-RC, Riyadh, Saudi Arabia from June 1990 to June 2013 were included.

All included patients fulfilled at least 4 of the American College of Rheumatology (ACR) classification criteria for SLE (17). Diagnosis of SLE was made before the age of 14 years old with minimal follow-up period of 1 year in the adult rheumatology clinic at KFSH- RC, Riyadh. Drug-induced lupus, mixed connective tissue disease and overlap syndrome were excluded from the study.

Medical records of all included patients were reviewed for demographic data, age, disease duration, clinical and laboratory findings at the last follow-up visit. The social, educational and employment status were recorded by a personal or phone interview at the last follow-up visit. The disease duration was calculated from the onset of symptoms related to SLE.

Patients are usually seen and evaluated every 3-6 months with a thorough physical examination and appropriate laboratory investigations.

To evaluate the disease activity at the last follow-up visit, we used the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) for disease activity. In contrast, to determine the long-term clinical outcome, we used the paediatric adaptation of the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index (pSDI) for ac-

crual disease damage (18). Growth failure and puberty delayed are of critical importance in children and adolescents with SLE. Additionally, death related to SLE was considered as an outcome measure.

Statistical methods

SAS 9.2 (SAS Institute Inc., Cary, NC, USA) software was used for statistical analysis. The variables compared using 2-sample *t*-tests, chi-square tests and Fisher's exact tests. The results expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Regression analysis was carried out to examine the influence of the variables on the outcome measures. A *p*-value of <0.05 was considered significant.

Results

Forty-eight patients (45 female) with disease onset under the age of 14 years were included. The mean age at diagnosis was 10.3±6 while the mean age at the time of enrollment was 23.6±4 years with mean disease duration of 15±4 years. All patients had chronic disease with relapse remitting course.

Table I summarises the demographic and clinical data at the diagnosis of SLE and the last follow-up visit.

At the last follow-up visit, 31 patients had haematological manifestations in the form of leukopenia or thrombocytopenia. Seventeen patients had active mucocutaneous features and 15 patients had musculoskeletal complaints. Furthermore, 40 (83%) patients had renal involvement, 20 patients with class IV, 13 patients with class III and 7 patients with class V. Central nervous system (CNS) involvement was found in 16 patients (33%) in the form of seizure disorder (6 patients), chorea (3 patients) and cerebrovascular accident (3 patients). All patients had anti-nuclear antibody positivity while 45 patients showed elevated anti-ds-DNA titer and 31 patients had low complement (C_3/ C_4) levels. Twenty-four, (50%) patients were found to have active disease; the mean SLEDAI score at the last follow-up visit was 6±4 (0-23) comparing to 38 (79%) patients with active disease at the initial visits with mean SLEDAI score of 10±6.

Table I. Demographic and clinical findings in 48 adult patients with childhood-onset SLE at diagnosis and last follow-up visit.

	At diagnosis	Last follow-up visit
Age (mean ± SD years)	10.3 ± 6	23.6 ± 4
Haematological	41 (85.4%)	31 (64.5%)
Cardiovascular	7 (14.5%)	5 (10.4%)
Musculoskeletal	31 (64.5%)	15 (31.3%)
Mucocutaneous	36 (75%)	17 (35.4%)
Nephritis	35 (73%)	40 (83.3%)
Neuropsychiatric	11 (23%)	16 (33.3%)
Antinuclear antibody	48 (100%)	48 (100%)
Anti-ds-DNA	47 (98%)	45 (94.8%)
Complement (C_3/ C_4)	38 (79%)	31 (64.5%)
No. of patients with active disease	38 (79%)	24 (50%)
No. of patients with pSDI >0	3 (6.3%)	39 (81%)

Table II shows the detailed immunosuppressive treatment. All the patients were treated with steroid, hydroxychloroquine and immunosuppressive drugs during their follow-up; 36 (75%) patients received intravenous cyclophosphamide, 28 patients received mycophenolate mofetil, 18 patients received azathioprine, 3 patients received rituximab, 3 patients received methotrexate, 5 patients received intravenous immunoglobulin (IVIG) and 4 patients required plasma exchange. The main indication of immunosuppressive therapy was renal involvement mainly class IV followed by CNS involvement. Four patients with inactive disease discontinued steroid and immunosuppressive treatment but continued hydroxychloroquine.

Thirty-four, (71%) patients completed high school, 21 of them joined a college and only 6 patients were in employment. Eight patients got married; 5 of them had children. In contrast, 4 patients had a miscarriage.

Table III showed the number of patients with damage and affected organ systems. Overall, 39 (81%) patients had disease damage, with mean accrual damage index of 2.1±1.7 (0-7). The higher SLEDAI score associated with accrual damage. However, it was not statistically significant (p=0.062). In contrast, the disease damage score correlated positively with disease duration (p=0.003). Twenty-four, (50%) patients had significant short stature and 13 (27%) had delayed puberty. Furthermore, 12 patients had renal damage, 7 (14.6%) had progressive renal disease and required dialysis, 5 patients underwent renal transplant (one died, 2 patients failed the transplant and are currently on haemodialysis, 2 patients with chronic graft rejection). Nine patients had neuropsychiatric damage, mainly due to cerebrovascular accident, and 9 patients had musculoskeletal sequelae because of osteomyelitis, avascular necrosis or severe osteoporosis associated with vertebral compression fracture.

The patient survival rate in this cohort was 93.75%. There were 3 (6.25%) deaths during the period of follow-up: two died due to infection, one due

Table II. The main treatments administered during follow-up period and their frequency.

	Number (%)
Cyclophosphamide	36 (75)
Mycophenolate mofetil	28 (58)
Azathioprine	18 (37.5)
Rituximab	3 (6)
Methotrexate	3 (6)
IVIG	5 (10)
Cyclosporine	4 (8)
Plasma exchange	4 (8)

Table III. Number of patients with damage and affected organ systems.

Organ system	Patient's Number
Growth retardation	24
Delayed puberty	13
Renal	12
Neuropsychiatric	9
Cardiovascular	6
Musculoskeletal	9
Skin	2

to opportunistic infection (candida glabrata sepsis) and other due to respiratory syncytial virus A complicated by refractory adult respiratory distress syndrome, and pulmonary haemorrhage. The third patient died outside our hospital with limited information on the cause of death.

Discussion

Survival of children with SLE has improved significantly over the last two decades (12, 19, 20). Accordingly, children with SLE might grow into adults with considerable morbidity resulting from social, educational, employment limitations and irreversible cumulative organ damage (13). These likely consequences are due to different reasons including long disease duration and disease severity in addition to long-term exposure to corticosteroids and immunosuppressive medications.

Outcome evaluation has been a focus of recent research in paediatric rheumatic diseases (7, 11, 12). Standardised outcome measures in childhood-onset SLE stress on organ involvement and overall survival. However, the same progress in social and functional aspects has not been achieved yet (21, 22). Nevertheless, recent longitudinal and cross-sectional cohort studies revealed a favourable prognosis of adult patients with childhood-onset SLE. However, the available data are limited (23, 24). Furthermore, due to increased risk of cumulative disease damage, childhood-onset SLE considered one of the important predictors of early morbidity and mortality in adult patients with childhood-onset SLE (25).

To the best of our knowledge, this is the first study from the Middle East that has addressed the outcome of adults with childhood-onset SLE.

In this retrospective study, we examined the long-term outcomes of 48 adult patients with childhood-onset SLE with mean disease duration of 15 years. At the last follow-up visit, half of the patients had active disease. Patients are more likely to have renal disease: 83% of the patients had nephritis, and 15% required dialysis. We found that 33% of our patients had neuropsychiatric manifestations; seizure disorder was the most frequent complaint. These findings are similar to previous observations (20, 26, 27). Furthermore, overall cumulative disease damage in our cohort is comparable to the former reports (5, 28). In fact, we believe that the cumulative damage is probably less in our patients especially we used pSDI as an outcome measure in our cohort. It is worth mentioning that pSDI considered growth retardation and delayed puberty as damage outcome domains in children with SLE.

Most of our patients with disease damage had ongoing disease activity which is consistent with the recognised observation of the longer disease duration and unremitting disease activity increased the risk of cumulative disease damage (28). Approximately 9–26% of SLE patients with renal disease progressed to renal failure similarly during the follow-up period – 14.5% of our patients with active renal disease progressed to end stage renal disease (20, 28). Our findings suggest that longer disease duration and probably SLEDAI score at the initial visits have significant predictive value in adult patients with childhood-onset SLE.

Childhood-onset SLE was found to be a strong predictor of mortality in a large cohort of SLE (23). The overall mortality related to SLE during the period of follow-up in our cohort was within the range of the previous reports. Infection was the most common cause of death probably due to intensive immunosuppressive therapy, the same findings observed in cohorts of childhood SLE (16, 19).

Data on health-related quality of life and functional status of adult patients with childhood-onset SLE are limited. Few reports have highlighted compromised health-related quality of life, school and employment performance in patients with patients with childhood-onset SLE (13, 28).

Two-thirds of our patients completed high school, and half of them joined a college. The majority of our patients were female; culturally, it is accepted for a female to be housewife even if she is able to work. So it is hard to conclude that unemployment was due to disease-related incapability. Quality of life is an essential item needs to be considered in patient assessment. Unfortunately, we could not assess the quality of life of our patients since a validated Arabic version of Lupus Quality of Life is not available.

Obviously, we did not attempt to assess the efficacy of treatment in this study. Nevertheless, we did not find any association between treatment and damage. Unfortunately, we could not draw a relationship between specific immunosuppressive medications and renal damage.

Overall, our results indicate that the outcome of adult patients with childhood-onset SLE was satisfactory and comparable to previous reports. It is obvious that further effort needs to be made to clarify the status of health-related quality of our patients. We believe that long-term prospective longitudinal study is crucial to understand the impact of childhood-onset SLE on adult patients.

References

1. BRUNNER H, HUGGINS J, KLEIN-GITELMAN M: Pediatric SLE-towards a comprehensive management plan. *Nat Rev Rheumatol* 2011; 4: 225-33.
2. SCHALLER J: Lupus in childhood. *Clin Rheum Dis* 1982; 8: 219-28.
3. BONO L, CAMERON J, HICKS J: The very long-term prognosis and complications of lupus nephritis and its treatment. *Q J Med* 1999; 92: 211-8.
4. CHIANG L, LIN Y, CHAN H, CHIANG B: Differential manifestations of prepubescent, pubescent and postpubescent pediatric patients with systemic lupus erythematosus: A retrospective study of 96 Chinese children and adolescents. *Pediatr Rheumatol Online J* 2012; 10: 12.
5. BRUNNER H, GLADMAN D, IBAÑEZ D, UROWITZ M, SILVERMAN E: Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum* 2008; 58: 556-62.
6. PAPADIMITRAKI E, ISENBERG D: Childhood- and adult-onset lupus: an update of similarities and differences. *Expert Rev Clin Immunol* 2009; 5: 391-403.
7. TUCKER L: Outcome measures in childhood rheumatic diseases. *Curr Rheumatol Rep* 2000; 2: 349-54.
8. MIETTUNEN P, ORTIZ-ALVAREZ O, PETTY R, CIMAZ R, MALLESON P, CABRAL D: Gender and ethnic origin have no effect on long-term outcome of childhood-onset systemic lupus erythematosus. *J Rheumatol* 2004; 31: 1650- 4.
9. AL-MAYOUF SM, AL SONBUL A: Influence of gender and age of onset on the outcome in children with systemic lupus erythematosus. *Clin Rheumatol* 2008; 27: 1159-62.

10. VACHVANICHSANONG P, DISSANEEWATE P, MCNEIL E: Twenty-two years' experience with childhood-onset SLE in a developing country: are outcomes similar to developed countries? *Arch Dis Child* 2011; 96: 44-9.
11. DUFFY C: Health outcomes in pediatric rheumatic diseases. *Curr Opin Rheumatol* 2004; 16: 102-8.
12. RAVELLI A, RUPERTO N, MARTINI A: Outcome in juvenile onset systemic lupus erythematosus. *Curr Opin Rheumatol* 2005; 5: 568-73.
13. CHALOM E, PERIERA B, COLE R, RETTIG P, DEHORATIUS R, ATHREYA B: Educational, vocational and socioeconomic status and quality of life in adults with childhood-onset systemic lupus erythematosus (long term quality follow up data from a single pediatric center). *Pediatr Rheumatol Online J* 2004; 2: 207-26.
14. MARKS S, TULLUS K: Modern therapeutic strategies for paediatric systemic lupus erythematosus and lupus nephritis. *Acta Paediatr* 2010; 99: 967-74.
15. HAGELBERG S, LEE Y, BARGMAN J *et al*.: Long-term follow-up of childhood lupus nephritis. *J Rheumatol* 2002; 12: 2635-42.
16. AL-MAYOUF S: Systemic Lupus Erythematosus in Saudi children: long-term outcomes. *Int J Rheum Dis* 2013; 16: 56-60.
17. TAN E, COHEN A, FRIES J *et al*.: The 1982 revised criteria for the classification of the systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
18. GUTIÉRREZ-SUÁREZ R, RUPERTO N, GASTALDI R *et al*.: A proposal for a pediatric version of the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index based on the analysis of 1,015 patients with juvenile-onset systemic lupus erythematosus. *Arthritis Rheum* 2006; 54: 2989-96.
19. LACKS S, WHITE P: Morbidity associated with childhood systemic lupus erythematosus. *J Rheumatol* 1990; 17: 941-5.
20. LEE P, YEH K, YAO T, LEE W, LIN Y, HUANG J: The outcome of patients with renal involvement in pediatric onset systemic lupus erythematosus - a 20 year experience in Asia. *Lupus* 2013; 22: 1534-40.
21. RUPERTO N, BURATTI S, DUARTE-SALAZAR C *et al*.: Health-related quality of life in juvenile-onset systemic lupus erythematosus and its relationship to disease activity and damage. *Arthritis Care Res* 2004; 51: 458-84.
22. MORTHY L, PETERSON M, HASSETT A, BARATELLI M, LEHMAN T: Impact of lupus on school attendance and performance. *Lupus* 2010; 19: 620-7.
23. HERSH A, TRUPIN L, YAZDANY J *et al*.: Childhood-onset disease as a predictor of mortality in an adult cohort of patients with systemic lupus erythematosus. *Arthritis Care Res* (Hoboken) 2010; 62: 1152-9.
24. MOK C, WONG S, MA K: Childhood-onset disease carries a higher risk of low bone mineral density in an adult population of systemic lupus erythematosus. *Rheumatology* (Oxford) 2012; 51: 468-75
25. HERSH A: Adult outcomes of childhood-onset rheumatic diseases. *Nat Rev Rheumatol* 2011; 5: 290-5.
26. MUSCAL E, BREY R: Neurological manifestations of systemic lupus erythematosus in children and adults. *Neurol Cli*n 2010; 1: 61-73.
27. YU H, LEE J, WANG L, YANG Y, CHIANG B: Neuropsychiatric manifestations in pediatric systemic lupus erythematosus: a 20-year study. *Lupus* 2006; 15: 651-7.
28. HERSH A, SCHEVEN E, YAZDANY J *et al*.: Differences in long-term disease activity and treatment of adult patients with childhood -and adult-onset systemic lupus erythematosus. *Arthritis Rheum* 2009; 61: 13-20.