Systemic lupus erythematosus in Arab children

Differences and similarities with different ethnicities

Ashwaq A. Ale'ed, *MD,* ***Sulaiman M. Al-Mayouf,*** *MD.*

ABSTRACT

الأهداف: وصف الميزات والمظاهر الذئبة الحمامية بين الأطفال العرب ومقارنتها مع مثيلاتها من الأعراق المختلفة.

الطريقة: أجري بحث شامل لجميع البحوث باللغة الإنجليزية التي نشرت عن الذئبة الحمامية لدى الأطفال العرب في مارس2013م. تمت مقارنة المظاهر السريرية والمخبرية بين الأطفال من مختلف الدول العربية وكذلك مع ما تم نشره عن الذئبة الحمامية لدى الاطفال من القوقاز وجنوب شرق آسيا.

النتائج: كان عدد الأطفال 560 من 5 دول عربية مع نسبة الذكور:الإناث1:5. وكان متوسط العمر عند التشخيص 10 أعوام. وصل تكرار الذذبه الحمامية العائلية إلى 30%. وكانت المظاهر السريرية الأكثر شيوعاً هي التهاب الجلد والأغشية المخاطية (88%)، التهاب المفاصل (75%)، التهاب الكلى(80%) في حين أن مظاهر الجهاز العصبي بلغت30% . تم استعمال الأدوية المثبطة للمناعة لدواعي مختلفة. لا يمكن من البيانات المتاحة تحديد النتائج النهائية للمرض. ومع ذلك، كان 145 من أصل 300 مريض عانوا من تأثر بالغ. توفي 40 مريضاً أثناء المرض يرجع في معظمه إلى التهابات ميكروبيه حادة.

الخاتمة: الذئبة الحمامية مألوف بين الأطفال العرب، خصوصاً الذئبة الحمامية العائلية. تواتر مظاهر المرض في الأطفال العرب مشابه للتقارير السابقة . هناك اختلاف ملحوظ، في شدة المرض ومعدل وفيات بين الأطفال العرب مقارنة بالأطفال الكنديين، والتي قد تعكس شدة المرض.

Objectives: To describe systemic lupus erythematosus (SLE) features among Arab children, and compare with cohorts from different ethnicities.

Methods: This retrospective analysis of all published English literature on SLE in Arab children was conducted in March 2013. The percentage and frequencies of the clinical and laboratory features were collected, and compared between different Arab countries as well as Caucasian and South East Asian cohorts.

Results: A total of 560 children from 5 Arab cohorts with an average age at diagnosis of 10 years; 7.7% of patients were diagnosed before the age of 5 years. Familial SLE was frequent. Most patients had major organ involvement. Renal involvement was diagnosed in 80%, while neuropsychiatric manifestations were seen in 30%. Immunosuppressive agents were commonly used. Beta cell depletion was recently introduced for refractory cases. The outcome of the disease could not be determined from the available data. However, 145 out of 300 patients had disease damage (52.6% Saudi and 43.9% Egyptian) with mean of 1.3 for Saudi and 0.93 for Egyptian. Forty patients died during the disease course due to infections and severe organ disease.

Conclusion: Systemic lupus erythematosus is common in Arab children, particularly familial SLE. The manifestations observed in Arabs are comparable with previous reports. However, there is a noticeable difference in the damage accrual and mortality rate between Arab and Canadian studies, which might reflect the disease severity.

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From the Section of Rheumatology, Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Sulaiman M. Al-Mayouf, Consultant and Section Head, Section of Rheumatology, Department of Pediatrics, MBC-58, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Kingdom of Saudi Arabia. Tel. +966 (11) 4427761. Fax. +966 (11) 4427784. E-mail: mayouf@kfshrc.edu.sa

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Systemic lupus erythematosus (SLE) is an inflammatory disorder of autoimmune origin, characterized by multi-system involvement. Systemic lupus erythematosus predominantly affects young women of reproductive age. However, 20% of all cases of SLE begin in childhood.[1,2] Clinical features of SLE at presentation and during disease course are different in children and adults. Furthermore, children are more likely to have major organ involvement and probably have often a graver prognosis than adults, which indicate the influence of age at onset on the clinical course and outcome of SLE.[3-5] The clinical manifestations of SLE have been extensively described from different geographical parts of the world; the prevalence and severity of the disease differ among ethnic groups.[6-9] Studies of SLE among Arab children are scarce.[10-16] Cohorts from Arab countries are descriptive and retrospective from single center experience. Unfortunately, the outcome of SLE is poorly studied. A systemic review of all published studies from Arab countries can determine the similarities among Arab children from different countries, and compare them with other series from different ethnic groups. Genetic factors may contribute into the clinical presentation and outcome in the Arab population, particularly in the presence of high consanguinity rate. This study evaluated the demographic, clinical, and laboratory features of SLE among Arab children.

Methods. In March 2013, we conducted a comprehensive literature search of all published studies of SLE among Arab children. The took place at Riyadh, Saudi Arabia. All English medical literature between 1990 and 2012 were reviewed to identify relevant articles. We used the following MeSH terms for the literature search: Arabs, Arabia, children, and systemic lupus erythematosus.

The included children meet the following criteria: Arab ethnicity and definite diagnosis of SLE using the Systemic Lupus International Collaborating Clinic classification criteria for SLE.[17] Children with drug-induced SLE, and other connective tissue diseases such as overlap syndrome were excluded. The collected data included gender, age at diagnosis, clinical and laboratory features through out the disease course including constitutional, mucocutaneous, articular, nervous system, renal, cardiac, pulmonary and gastrointestinal tract findings and hematogram, acute phase reactants, antinuclear antibody (ANA), extractable nuclear antigen antibody (ENA), anticardiolipin (aCL) or anti-ß2 glycoprotein-1 (ß2-GP-I) and complement levels. Nephritis was defined by histopathology according to the World Health Organization (WHO) classification as well as unusual co-morbidity and mortality associated with the disease. The percentage and frequencies of the clinical and laboratory features were collected, and compared between different Arab countries as well as Caucasian and South East Asian cohorts.

Statistical analysis. The Statistical Analysis Software version 9.2 (SAS Institute Inc., Cary, NC, USA) software was used for statistical analysis. The results were expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. The variables were compared by 2-sample t-tests, Chi-square tests, and Fisher's exact tests. A *p*-value of <0.05 was considered significant.

Results. Data was retrieved from 7 retrospective studies; the study duration varied between 7 to 20 years. Two studies were not considered independently;[18,19] however, patients from these studies were included in the updated cohorts.[13,16] A total of 560 children with SLE were reported from 5 different Arab countries (Bahrain, Egypt, Kuwait, Oman, and Saudi Arabia); the highest number of patients was from Egypt (n=207) and Saudi Arabia (n=182).[13,15,16]

The mean follow up duration was 4.3±3.2 years, ranging between 2 and 7 years. Girls were more frequently affected; the female to male ratio ranged from 2.5:1 to 5.6:1. However, 2 reports had the highest ratio with female to male ratio of 14:1. The mean age at diagnosis was 10±6.7 years (range 8.6-10.7). Among 443 patients from 4 studies (Saudi Arabia, Egypt, Oman, Bahrain), the disease was diagnosed before the age of 5 years (7.7%). The frequency of familial SLE cases from the same cohorts was variable, from 2.9-36%. Interestingly, the Saudi cohort showed that the frequency of affected siblings was 18.5%. **Table 1** summarizes the main demographic data of 7 cohorts.[10-16]

Most patients had major organ involvement. **Table 2** shows the clinical manifestations observed in different Arab cohorts. The most frequent clinical manifestations throughout the course of the disease were mucocutaneous (40-88%) and musculoskeletal (40-75%). Most mucocutaneous manifestations were oral ulcerations, malar rash, and alopecia. Most patients with musculoskeletal had polyarthritis affecting mainly the small joints; it was non-deforming and symmetrical arthritis. Constitutional symptoms were in the form of fever, fatigue, and weight loss observed frequently and reported in 80% of patients. Renal involvement was diagnosed in 28-80% of patients. Hematuria and proteinuria were the most frequent findings. According to the WHO classification, almost 40% of patients

Table 1 - Comparison of demographic data of childhood SLE in 6 Arab countries and with their counterpart (Canada and Philippines).

Demographic data	Kuwait Alsaeid[10]	Egypt Salah[13]	Egypt Bakar[11]	Saudi Arabia Al-Mayouf[16]	Saudi Arabia Muzaffer[15]	Oman Abdwani[12]	Bahrain Al-Mosawi[14]	Canada Hiraki[26]	Philippines Gulay[27]
Number of patients	35	207	52	152	30	50	34	256	78
Gender (Female:male)	4:1	2.7:1	12:1	5.6:1	14:1	5.3:1	2.5:1	4.7:1	10:1
Age at onset (mean)	NA	10	NA	8.8	10.5	8.6	9	NA	NA
Age at diagnosis (mean)	10.7	10	11.9	9.5	10.5	8.6	9	13.1	14
Disease duration (mean)	NA	6.5	5	7.5	NA	NA	7	NA	NA
Follow up duration (mean)	NA	NA	2.1	6.8	6	NA	NA	3.5	1.7
Study duration (year)	7	16	7	20	10	16	10	23	5
Family history (%)	NA	2.9[b]	NA	18.5[b]	NA	36[a]	25[a]	NA	10.2

a - relatives with SLE, b - affected siblings, NA - not applicable

Table 2 - Comparison of clinical and laboratory findings of childhood SLE in 6 countries and with their counterpart (Canada and Philippines).

Clinical and laboratory findings	Kuwait Alsaeid[10]	Egypt Salah[13]	Egypt Bakar[11]	Saudi Arabia Al-Mayouf[16]	Saudi Arabia Muzaffer[15]	Oman Abdwani[12]	Bahrain Al-Mosawi[14]	Canada Hiraki[26]	Philippines Gulay[27]
Number of patients	35	207	52	152	30	50	34	256	78
Arthritis	15 (42.9)	82 (39.6)	34 (65.4)	81 (53.3)	22 (73.3)	38 (76.0)	21 (61.8)	171 (67.0)	42 (53.8)
Cardiac	2 (5.7)	35 (16.9)	4 (7.7)	24 (15.8)	3 (10.0)	5 (10.0)	7 (20.6)	46 (17.9)	17 (21.8)
Constitutional (any)	NA	62 (29.9)	40 (80.0)	118 (77.6)	15 (50.0)	31 (62.0)	NA	142 (55.5)	NA
Hematological									
Hemolytic anemia	7 (20.0)	40 (19.3)	26 (50.0)	76 (50.0)	8 (26.7)	30 (60.0)	14 (41.2)	63 (25.6)	8 (10.2)
Thrombocytopenia	8 (23.0)	45 (21.7	14 (26.9)	60 (39.5)	4 (13.3)	NA	18 (52.9)	80 (31.2)	20 (25.6)
Leucopenia	NA	54 (26.1)	14 (26.9)	72 (47.4)	10 (30.3)	NA	14 (41.2)	NA	25 (32.1)
Lymphadenopathy	3 (8.6)	NA	NA	60 (39.5)	10 (30.3)	18 (36.0)	NA	51 (20.0)	NA
Mucocutaneous									
Cutaneous	18 (51.4)	100 (48.3)	24 (46.2)	114 (75.0)	14 (46.7)	35 (70.0)	30 (88.2)	169 (66.0)	60 (76.9)
Mucosal	10 (28.6)	46 (22.2)	10 (19.2)	85 (55.9)	1 (3.3)	5 (10.0)	3 (8.8)	76 (29.7)	53 (67.9)
Photosensitivity	NA	91 (44.0)	11 (21.2)	24 (15.8)	5 (16.7)	NA	6 (17.6)	52 (20.3)	57 (73.1)
Alopecia	NA	93 (45.0)	18 (34.6)	67 (44.1)	9 (30.0)	35 (70.0)	NA	73 (28.5)	41 (52.6)
Nephritis	10 (28.6)	139 (67.1)	42 (80.8)	90 (59.2)	22 (73.3)	32 (64.0)	15 (44.1)	141 (55.1)	56 (71.8)
Neuropsychiatric	5 (14.3)	50 (24.2)	4 (7.7)	34 (22.4)	9 (30.0)	9 (18.0)	10 (29.4)	68 (26.5)	25 (32.1)
Pulmonary	3 (8.6)	13 (6.3)	NA	12 (7.9)	2 (6.7)	13 (26.0)	7 (20.6)	39 (15.2)	17 (21.8)
ANA	35 (100)	196 (94.7)	38 (73.1)	152 (100)	30 (100)	50 (100)	29 (85.3)	256 (100)	70 (98.1)
Anti-dsDNA	31 (88.6)	96 (46.4)	44 (84.6)	135 (88.8)	27 (90.0)	41 (82.0)	21 (61.8)	214 (83.6)	18/21
APL									
ACL IgM	13 (37.1)	36/108	NA	45/130	10/15	NA	2/ 15	NA	NA
ACL IgG	11 (31.4)	26/108	NA	65/130	10/15	NA	4/ 15	102/254	NA
ß2-glycoprotein I	NA	NA	NA	31/92	NA	NA		NA	NA
Lupus anticoagulant		30/108	NA	NA	NA	NA		32/254	NA
C3	22 (62.9)	NA	31 (59.6)	118 (77.6)	22 (73.3)	42 (84.0)	NA	NA	7 (8.9)
C4	22 (62.9)	NA	NA	118 (77.6)	22 (73.3)	40 (80.0)	NA	NA	NA
pSDI	NA	0.93	NA	1.3	NA	NA	NA	0.6	NA
Mortality	3 (8.6)	11 (5.3)	8 (15.4)	9 (5.9)	3 (10.0)	2 (4.0)	4 (11.8)	6 (2.3)	9 (11.5)

ANA - antinuclear antibody, Anti-dsDNA - antidouble stranded DNA, APL - anti phospholipid antibody, ACL - anti cadriolipin, pSDI - pediatric adaptation of the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index

with nephritis had class IV nephritis. Neuropsychiatric manifestations including seizures, stroke, mood affection, and rarely neuropathy and myelitis were seen in 30% of patients. Cardiac (15%) and pulmonary manifestations (<10%) were the least frequent clinical manifestations. However, 26% of Omani patients were found to have pulmonary involvement. Most patients had hemolytic anemia, thrombocytopenia, and leucopenia appearing concurrently. Throughout the disease course, ANA was detected in almost all patients. However, 96% of patients had raised anti-double stranded DNA antibody (anti-dsDNA) levels. Furthermore, anti-phospholipid antibody (either aCL or ß2-GP-I) was observed in 30-40% of patients. Unfortunately, other extractable nuclear antigens (ENA) levels were not reported. Hypocomplementemia (C_3 and C_4) were noticed in almost 85% of patients. Interestingly, 13 Saudi children were found to have C1q deficiency.

Table 2 compares the clinical and laboratory findings of childhood SLE in Arab countries. Treatment

regimens were available in 441 patients from 4 cohorts (2 Saudi and 2 Egyptian). All patients were treated with glucocorticoids and hydroxychloroquine. Immunosuppressive agents (cyclophosphamide, azathioprine, mycophenolate mofetil) were commonly used for various indications. However, the major organ disease namely renal and neuropsychiatric involvements were the most frequent indications. Intravenous pulse cyclophosphamide was used as induction and maintenance therapy in 198 (44.9%) of the Saudi and Egyptian cohorts. Mycophenolate mofetil and azathioprine were used mainly as a maintenance treatment after completion of induction cyclophosphamide regimen. However, mycophenolate mofetil was used in combination with corticosteroids for induction of remission in 43 Saudi patients, while 30 Saudi patients received azathioprine in combination with corticosteroids as first-line therapy. However, in 26 patients, treatment with mycophenolate mofetil or azathioprine switched to cyclophosphamide due to inefficacy. In contrast, mycophenolate mofetil was used in 16 Egyptian patients to induce remission after failure of cyclophosphamide. The beta cell depletion was used for refractory cases; 25 Saudi patients were treated with rituximab. Additional and supportive therapy were used when needed, such as intravenous immunoglobulin infusion, plasmapheresis, antihypertensive medications, and diuretics. The eventual outcome of the disease could not be appropriately determined from the available data. However, 145 (80 Saudi and 65 Egyptian) out of 359 patients had disease damage as measured by the pediatric adaptation of the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index (pSDI); it was reported in 52.6% of Saudi (mean: 1.3+1.7) and 43.9% (mean: 0.93+1.37) of Egyptian patients. Damage accrual in Saudi patients was mostly in the growth (26.8%), renal (17.1%), and neuropsychiatric (15.8%) domains, while neuropsychiatric (21%) and renal (16.9%) system involvement were observed most frequently in Egyptian patients.[13,16]

Out of 389 patients, 28 (14 Saudi, 14 Egyptian) patients had progressive renal disease and required dialysis. Forty patients died during the disease course mostly due to infections and severe organ disease.[11,13,16] Chronic renal failure and end stage renal disease was the most frequent cause of death following the infections. Few patients died due to intracranial hemorrhage, cardiac failure, or pulmonary hemorrhage.

Discussion. Systemic lupus erythematosus is a multi-system disease characterized by frequent disease flares. The overall prognosis has markedly improved over the last 2 decades.[20] The prevalence and severity of the disease differ among ethnic groups; compared with Caucasian children with SLE, non-Caucasian patients were significantly younger and more likely to have nephritis.[8,9] Though there are numerous reports of SLE in children worldwide, limited data on childhood SLE from Arab countries have been published. The available published English medical reports were from 5 countries: Egypt, Saudi Arabia, Kuwait, Oman, and Bahrain. Unfortunately, we could not find data from North Africa or other Middle Eastern countries. All these reports were retrospective studies from a single center cohort. The total number of patients was 560; the mean age of onset and diagnosis were comparatively similar. The female to male ratio was approximately 4:1. However, 2 cohorts had higher frequency (female patients) (more than 10:1). Interestingly, familial SLE cases are commonly seen in Arabs; the rate of familial SLE is higher in Arabs compared with the Caucasian ethnicity. The consanguinity rate in Arab countries is common (Saudi Arabia 58%), which might play a role in the apparent increased frequency of SLE in Arab families.[21] Familial SLE patients were first-degree relatives; remarkably previous study[22] had the highest frequency of affected siblings with 18.5%. Previous study[22] suggested that familial SLE patients tend to be younger and more likely to have discoid rash with more frequent complement (C1q) deficiency; furthermore, they had higher rate of mortality compared with sporadic cases. However, similar findings were not confirmed from the Omani cohort. Nonetheless collaborative work between the Saudi and Omani groups, illustrated a number of families with high degrees of clustering of childhood onset SLE in a rare autosomal recessive form that was very helpful in identifying patients with a stronger genetic predisposition. Successfully, autozygome analysis in those families revealed a null mutation in the DNASE1L3 gene. Interestingly, the DNASE1L3-related SLE described was always pediatric in onset and correlated with a high frequency of lupus nephritis. These findings confirm the critical role of impaired clearance of degraded DNA in SLE pathogenesis.[23-25]

Difference in the clinical manifestations among Arab children with SLE were not major, and the frequency of clinical and laboratory variables including major organ involvement and autoantibody profiles to some extent were comparable (p>0.05). Five cohorts

reported nephritis in more than 50% of their patients; progressive proliferative nephritis was most commonly seen in Arab childhood SLE.

We compared the cumulative manifestations of Arab SLE children with 2 cohorts of different ethnic backgrounds; Canadian (Caucasian) and Filipino (South East Asian), and similarities in disease manifestations were observed. However, there is a noticeable difference in the damage accrual between our series and the Canadian series (1.3 versus 0.6) with p=0.027.[26] Furthermore, the mortality rate was higher in our series compared with the Canadian cohort (5.9% versus 2.3%) (p=0.039), which might reflect the disease severity.[26,27] However, this needs further investigation.

Treatment approach was based on the overall disease activity and severity, and corticosteroids and hydroxycholraquine were the main stay of treatment. All patients received immunosuppressive drugs (cyclophosphamide, azathioprine, and mycophenolate mofetil); the main indication for using cyclophosphamide was class IV lupus nephritis, followed by neuropsychiatric manifestations. Recently, rituximab was introduced as a therapeutic option for the refractory cases. Despite the aggressive therapeutic approach, 7.2% out of 389 patients developed chronic renal failure.[11,13,16] The overall mortality related to SLE during the period of follow-up was within the range of reports from Asia.[27] However, it is slightly higher than the Canadian cohort.[26] Infection was the most common cause of death followed by chronic renal disease. Nevertheless, damage accrual was not systematically documented in Arab cohorts. However, 2 recent reports from Egypt and Saudi Arabia showed that the frequency and amount of damage observed are comparable with those reported in previous studies on childhood onset SLE.[16,28]

Study limitations. This study has some limitations due to the nature of the available data. The number of patients in various studies was small and varied greatly in terms of incomplete results and inconstant treatment regimens, and the time span of studies varied, which make comparisons between different studies difficult and interpretation imprecise.

In conclusion, we believe that SLE is common in Arab children, particularly familial SLE. These cohorts are descriptive, retrospective from a single center experience and representative for Arab childhood SLE. We believe that prospective multicenter efforts will provide better understanding of the long-term outcome of SLE among Arab children.

References

1. Brunner H, Huggins J, Klein-Gitelman M. Pediatric SLE-towards a comprehensive management plan. ***Nat Rev Rheumatol*** 2011; 7: 225-233.
2. Malattia C, Martini A. Paediatric-onset systemic lupus erythematosus. ***Best Pract Res Clin Rheumatol*** 2013; 27: 351-362.
3. Papadimitraki E, Isenberg D. Childhood- and adult-onset lupus: an update of similarities and differences. ***Expert Rev Clin Immunol*** 2009; 5: 391-403.
4. Livingston B, Bonner A, Pope J. Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. ***Lupus*** 2011; 20: 1345-1355.
5. Watson L, Leone V, Pilkington C, Tullus K, Rangaraj S, McDonagh J, et al. Disease activity, severity, and damage in the UK juvenile-onset systemic lupus erythematosus cohort. ***Arthritis Rheum*** 2012; 64: 2356-2365.
6. González L, Toloza S, McGwin G, Alarcón G. Ethnicity in systemic lupus erythematosus (SLE): its influence on susceptibility and outcomes. ***Lupus*** 2013; 22: 1214-1224.
7. Vina E, Masi C, Green S, Utset T. A study of racial/ ethnic differences in treatment preference among lupus patients. ***Rheumatology (Oxford)*** 2012; 51: 1697-1706.
8. Levy D, Peschken C, Tucker L, Chédeville G, Huber A, Pope J, et al. Influence of ethnicity on childhood-onset systemic lupus erythematosus: results from a multiethnic multicenter Canadian cohort. ***Arthritis Care Res (Hoboken)*** 2013; 65: 152-160.
9. Huang J, Yeh K, Yao T, Huang Y, Chung H, Ou L, et al. Pediatric lupus in Asia. ***Lupus*** 2010; 19: 1414-1418.
10. Alsaeid K, Kamal H, Haider M, Al-Enazi H, Malaviya A. Systemic lupus erythematosus in Kuwaiti children: organ system involvement and serological findings. ***Lupus*** 2004; 13: 613-617.
11. Bakr A. Epidemiology treatment and outcome of childhood systemic lupus erythematosus in Egypt. ***Pediatr Nephrol*** 2005; 20: 1081-1086.
12. Abdwani R, Rizvi S, El-Nour I. Childhood systemic lupus erythematosus in Sultanate of Oman: demographics and clinical analysis. ***Lupus*** 2008; 17: 683-686.
13. Salah S, Lotfy H, Sabry S, El Hamshary A, Taher H. Systemic lupus erythematosus in Egyptian children. ***Rheumatol Int*** 2009; 29: 1463-1468.
14. Al-Mosawi Z, Al-Hermi B, Al-Saad K, Farid E, Makki H. Juvenile systemic lupus erythematosus in Bahrain. ***Saudi Med J*** 2009; 30: 667-672.
15. Muzaffer M, Al-Mayouf SM. Clinical and laboratory variables of childhood systemic lupus erythematosus in western province of Saudi Arabia. ***Rheumatol Int*** 2011; 31: 23-26.
16. Al-Mayouf SM. Systemic lupus erythematosus in Saudi children: long-term outcomes. ***Int J Rheum Dis*** 2013; 16: 56-60.
17. Petri M, Orbai A, Alarcón G, Gordon C, Merrill J, Fortin P, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinic classification criteria for systemic lupus erythematosus. ***Arthritis Rheum*** 2012; 64: 2677-2686.
18. El-Garf A, Salah S. Juvenile systemic lupus erythematosus among Egyptian children. ***J Rheumatol*** 1990; 17: 1168-1170.
19. Bahabri S, Alsabban E, AlRashed A, Al-Mayouf S, AlMazyed A, Abdulrazik A, et al. Juvnile systemic lupus erythematosus in 60 Saudi children. ***Ann Saudi Med*** 1997; 17: 612-615.

20. Marks S, Tullus K. Modern therapeutic strategies for paediatric systemic lupus erythematosus and lupus nephritis. ***Acta Paediatr*** 2010; 99: 967-974.
21. El Mouzan M, Al Salloum A, Al Herbish A, Qurachi M, Al Omar A. Consanguinity and major genetic disorders in Saudi children: a community-based cross-sectional study. ***Ann Saudi Med*** 2008; 28: 169-173.
22. Al-Mayouf SM, AlSonbul A. Juvenile systemic lupus erythematosus in multicase families from Saudi Arabia: comparison of clinical and laboratory variables with sporadic cases. ***Lupus*** 2006; 15: 616-618.
23. Qari A, Al-Mayouf SM, Al-Owain M. Mode of Inheritance in Systemic Lupus Erythematosus in Saudi Multiplex Families. ***Genet Couns*** 2009; 20: 215-223.
24. Al-Mayouf SM, Abdomi R, Abrwai S. Familial juvenile systemic lupus erythematosus in arab children. ***Rheumatol Int*** 2012; 32: 19939-1943.
25. Al-Mayouf SM, Sunker A, Abdwani R, Al Abrawi S, Almurshedi F, Hashimi N, et al. Loss of function variants in DNASE1L3 confer risk of systemic lupus erythematosus. ***Nat Genet*** 2011; 43: 1186-1188.
26. Hiraki L, Benseler S, Tyrrell P, Hebert D, Harvey E, Silverman E. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. ***J Pediatr*** 2008; 152: 550-556.
27. Gulay C, Dans L. Clinical presentations and outcomes of Filipino juvenile systemic lupus erythematosus. ***Pediatr Rheumatol Online J*** 2011; 9: 7.
28. Salah S, Lotfy H, Mokbel A, Kaddah A, Fahmy N. Damage index in childhood-onset systemic lupus erythematosus in Egypt. ***Pediatr Rheumatol Online J*** 2011; 9: 36.

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Bansal RK, Kumar A, Bansal N, Arora A. Abdominal cocoon as a presenting feature of systemic lupus erythematosus. *A rare presentation.* ***Saudi Med J*** 2013; 34: 1189-1191.

Tyagi NK, Lahita RG. Therapeutic modalities in systemic lupus erythematosus. ***Saudi Med J*** 2013; 34: 887-895.

Al-Shobaili HA, Rasheed Z. Immunological studies of oxidized superoxide dismutase in patients with systemic lupus erythematosus. *Correlation with disease induction and progression.* ***Saudi Med J*** 2012; 33: 1177-1184.