Juvenile systemic lupus erythematosus in Bahrain

A tertiary referral center experience

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ABSTRACT

الأهداف: تحليل العلامات السريرية والمصلية عند الأطفال المصابين بداء الذئب الحمامي الجهازي (SLE) في اكبر مركز علاجي في مملكة البحرين، كذلك لمعرفة الحالات المرضية الأخرى المصاحبة، وتقييم نسبة المضاعفات والوفيات المصاحبة للمرض.

الطريقة: تمت مراجعة ملفات الأطفال المصابين بداء الذئب الحمامي الجهازي (SLE)، والذين تم علاجهم في عيادة الأطفال لأمراض الروماتيزم – مركز السلمانية الطبي – مملكة البحرين، خلال الفترة مابين 1998م وحتى 2007م. وقد تم اعتماد هذه الدراسة من قبل لجنة الأبحاث في وزارة الصحة بمملكة البحرين.

النتائج: تم التعرف على 32 حالة مصابة بداء الذئب الحمامي الجهازي (SLE)، شكل البحرينيين 31 مريضاً (96.8%)، متوسط العمر 4±14 عام، ومتوسط عمر الأطفال في بداية المرض هو 4±9 عام، ومتوسط فترة المرض 5±7 عام. كانت نسبة الإناث إلى الذكور 1:2.5، وكان لـ(25%) من الحالات المرضية أقارب مصابين بداء الذئب الحمامي الجهازي (SLE)، و 8 مرضى (25%) كانوا مصابين بمرض فقر الدم المنجلي (SCA). أما فيما يتعلق بنسبة تأثر أجهزة الجسم المختلفة بالمرض فكانت كالتالي: الجلد (93%)، الكلى (81%)، الجهاز العضلي الهيكلي (65%)، الدم (56%)، الجهاز الهضمي والعصبي كلاً منهما بنسبة (31%)، الرئتين والقلب كلاً بنسبة (21%). أما بالنسبة للاختبارات المصلية فقد بينت الدراسة التالي: نتيجة (ANA) كانت ايجابية في (90.6%)، نسبة الـ anti ds DNA (65%)، نسبة المضاعفات (21%) في 7 حالات ، الوفيات (12.5%) 4 حالات.

خاتمة: أوضحت الدراسة إن كلاً من النتائج السريرية والمصلية لمرضانا مقاربة لنتائج الدراسات العالمية، ويشكل الالتهاب الكلوي الذئبي أحد الأسباب الرئيسية للمضاعفات والوفيات. تصاحب داء الذئب الحمامي الجهازي (SLE) بفقر الدم المنجلي (SCA) في دراسات سابقة، ويحتاج هذا التصاحب إلى دراسة جينية موسعة.

Objectives: To analyze the clinical and serological features of children with systemic lupus erythematosus (SLE) in a major referral center in Bahrain and to assess the comorbidity, its morbidity, and mortality.

Methods: We retrospectively reviewed the medical charts of children with SLE treated in the Pediatric Rheumatology Clinic at Salmaniya Medical Complex, Kingdom of Bahrain from 1998 to 2007. The ethical approval for the study was obtained from the Research Health Committee, Ministry of Health, Kingdom of Bahrain.

Results: Thirty-two children with SLE were identified. Thirty-one (96.8%) were Bahrainis. The mean age was 14±4 years, the mean age of disease onset was 9 ± 4 years and the mean duration of illness was 7 ± 5 years. The female to male ratio was 2.5:1. Twenty-five percent of the cases had relatives with SLE. Eight patients (25%) had sickle cell anemia (SCA). Systems involved were as follows: skin (93%), kidney (81%), musculoskeletal system (65%), blood (56%), gastrointestinal tract (31%), central nervous system (31%), lungs and cardiovascular system (21%). Serological tests showed: positive antinuclear antibody in 90.6%, and positive anti double-stranded DNA antibody in 65%. The morbidity rate was 21% (n=7) due to complication and 12.5% (n=4) died.

Conclusion: Clinical and serological results were comparable with the international studies. Nephritis was the primary cause of morbidity and mortality. Coexistence of SLE with SCA was also reported in other studies and may need further investigation with genetic studies.

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Systemic lupus erythematosus (SLE) is a chronic, autoimmune, multisystem disease that is estimated to occur in 10-20 per 100,000 children depending on the ethnic population.[1] Children with SLE generally have a more severe disease at onset and higher rate of organs involvements.[2] Salmaniya Medical Complex (SMC) is a tertiary referral hospital and the pediatric department caters for more than two thirds of pediatric patients in Kingdom of Bahrain. Pediatric rheumatology clinic receive patients below age of 16 years with the suspicion of SLE referred from the primary health care or private clinics for confirming diagnosis and follow-up. The objective of this study is to: analyze the clinical and serological features of children with SLE who attended rheumatology clinic at SMC between January 1998 and December 2007, to assess the associated co-morbidity as well as the morbidity and mortality associated with the disease, and to compare the clinical and the serological manifestations of patients in this study with the other published studies.

Methods. The medical records of all patients below the age of 16 years who fulfilled at least 4 of the 1997 revised American College of Rheumatology (ACR) criteria for the classification of SLE[3] and attended the Pediatric Rheumatology Clinic at SMC between January 1998 and December 2007 were reviewed. Ethical approval for the study was obtained from the Research Health Committee, Ministry of Health, Kingdom of Bahrain.

Data collected included biographic data, age at presentation of SLE and the duration of illness, family history of SLE, and the co-morbidity. Serology studies namely antinuclear antibody (ANA), anti double-stranded DNA (dsDNA) antibody, extractable nuclear antigen antibody (ENA), anti-cardiolipin antibody (ACL) and the complement assay were obtained. Detection of anti ds-DNA in our study was carried out by 2 techniques namely enzyme-linked immunosorbent assay (ELISA) and Crithidia luciliae immunofluorescent technique to avoid any false-positive results. Anticardiolipin antibodies of the IgG and IgM isotypes were measured by ELISA method. Results were reported as normal if <20 GPL and MPL units for IgG and IgM.[4]

Patients with nephritis documented by histopathology were graded according to the WHO classification.[5] Multi-systems involvement and the morbidity were reviewed, as well as the causes of mortality were studied. Neuropsychiatric (NP) manifestations were classified according to the 1999 American College of Rheumatology (ACR) classification system for Neuropsychiatric systemic lupus erythematosus (NPSLE).[6]

The Statistical Package for Social Sciences SPSS, version 15.0 was used for data analysis. Results were compared with the other international studies. Goodman and Kruskal's tau test was used for correlation of positive anti dsDNA antibody with nephritis and P-value was considered significant if below 0.05.

Results. Thirty-four pediatric patients with SLE were identified. Two cases (5.8%) were excluded as they did not fulfill the ACR classification criteria for diagnosing SLE.[3] All except one were Bahraini. The female to male ratio was 2.5:1. The age at presentation was 1.5-15 years with a mean of 9 ± 4 years; 2 children were <2 years of age at the time of diagnosis. The duration of illness with SLE ranged from 1-19 years with a mean of 7 ± 5 years. Eight patients (25%) had a positive family history of SLE. Three males and one female patient had an affected older sisters. Two girls had female cousins with SLE and another girl had paternal aunt with SLE. One male patient's mother had SLE. The co-morbidity with SLE was mainly genetic blood disorders. Eight patients (25%) had sickle cell anemia (SCA), 6 with sickle cell disease (SCD), and 2 with sickle cell trait (SCT). Glucose-6-phosphate dehydrogenase (G6PD) deficiency was reported in 5 patients (15%), and one patient had B-thalassemia major. One patient had Hashimoto thyroiditis in addition to SLE.

Clinical manifestations and systemic involvements were summarized in **Table 1**. Renal biopsy was performed in 15 patients. Results of biopsy, graded according to the WHO classifications of nephritis,[5] are summarized in **Table 2.**

Serological results were shown in **Table 3**. Anti dsDNA antibody was reported more in males than females (77.8% versus 61%). Two patients with anti SSA presented with same skin rash morphology; annular, psoriasform and discoid skin lesions in addition to lipodystrophy, while all patients with anti Sm antibody had nephritis. Anti-cardiolipin antibody was assessed in 13 patients; it was positive in 6 only; IgG type in 4 and IgM type in 2. Two patients with IgG ACL antibody had cerebrovascular disease; one of them had severe Reynard's phenomena and osteonecrosis as well. Two patients had a positive IgM ACL antibody (one had Evan's syndrome and one had recurrent transverse myelitis).

Treatment. For skin manifestations and arthritis we treated them with hydroxyl chloroquine (5-6 mg/kg, non-steroidal anti-inflammatory drugs (Naproxen 10-20 mg/kg/day) and corticosteroid therapy (prednisone 1-2 mg/kg/day). For nephritis we gave them corticosteroid (prednisone 0.5-2 mg/kd/day, azathioprine 1-2 mg/kd/day), intravenous cyclophosphamide (500-1000 mg/m^2/day; pulse therapy) cyclosporine (5-6 mg/kg/day), mycophenolate mofetil (1-3 g/day) and plasmapheresis

(2-3 times/week). B-cells depletion therapy was effective in one patient with uncontrolled grade IV nephritis. For other systemic manifestations such as CNS, CVS and lungs; corticosteroid was the main treatment of choice. By avoiding the use of oxidizing agents that trigger hemolysis crises, no significant complications was observed in treating patients with or without G6PD deficiency. No reported difficulties on managing the SLE patients with B thalassemia major.

Morbidity. Three patients with grade IV MPGN underwent repeated renal biopsy after 2 years of cyclophosphamide therapy and the results revealed no regression but rather chronic changes such as sclerosis in some glomeruli, focal tubular atrophy and arteriolosclerosis. Cognitive dysfunction following cerebrovascular disease in the first year of illness was reported in another 3 patients (a 9-year-old boy and 2 girls aged 3 and 6 years). On follow-up they were noticed to have attention deficit, difficulty in reasoning and problem solving, short memory and learning disability which hampered their school achievements. These patients could not manage in the ordinary school and were referred to a specialized rehabilitation center. One 10-year-old boy had severe joints deformity in ankles that prevented him from weight bearing and he was wheelchair-bound after the family refused any surgical interference. Osteoporosis developed in 2 patients and diabetes mellitus in one patient after prolonged use of corticosteroid therapy.

Mortality. Death was reported in 4 patients (12.5%) (aged 11, 16 and 18 years) and all had stage IV MPGN at the beginning of their illness associated with heavy proteinuria and persistent hypertension, followed by renal failure (**Table** 4). A 16-year-old girl diagnosed with cardiomyopathy in the first year of her illness, she responded initially to pulses of methlyprednisolone but later progressed to heart failure and died with multi-organ failure.

Table 1 - Cumulative frequencies of systemic involvement in 32 children with systemic lupus erythematosus.

Organ involved	No. of patients (N=32) (%)	
Mucocutaneous	30	(93)
Rash	30	(93)
Photosensitivity	6	(18)
Oral ulcer	3	(9)
Oncholysis	2	(6)
Kidney	26	(81)
Musculoskeletal system	21	(65)
Blood	18	(56)
Thrombocytopenia	18	(56)
Evan's syndrome	1	(3)
Anemia	14	(43)
Hemolytic anemia	6	(18)
Leucopenia	14	(43)
Gastrointestinal tract	10	(31)
Abdominal pain	4	(12)
Pancreatitis	1	(3)
Gastritis, GER	3	(9)
Peritonitis	2	(6)
Central nervous system	10	(31)
Aseptic meningitis	2	(6)
Seizure	3	(9)
Cognitive dysfunction	3	(9)
Headache	8	(25)
Depression/mood disorder	8	(25)
Chorea	1	(3)
Transverse myelitis	1	(3)
Cardiovascular system	7	(21)
Pericarditis	7	(21)
Cardiomyopathy	1	(3)
MR & AR	1	(3)
Lungs	7	(21)
Pleuritis	7	(21)
Interstitial pneumonia	1	(3)

GER - gastroesophageal reflux, MR- mitral regurgitation, AR -aortic regurgitation

Discussion. Systemic lupus erythematosus is a rare collagen vascular disease of unknown etiology.

Table 2 - Results of renal biopsy in 15 patients.

Grades of nephritis	No. of patients (N=15)
Mesangial nephritis (grade II)	2
Mesangio-proliferative glomerulo-nephritis (grade III)	3
Membrano-proliferative (MPGN) (grade IV)	9
Membranous GN (grade V)	1

Table 3 - Serology status of 32 patients with systemic lupus erythematosus.

Antibody	No. of patients (%)	
Antinuclear antibody	29	(90.6)
Anti double stranded DNA antibody,	21	(65)
Rheumatoid factor	2	(6)
Sjögren's syndrome antigen A	10	(3)
Sjögren's syndrome antigen B	3	(9)
Anti small nuclear ribonucleoprotein antibody.	8	(25)
Smith antibody	11	(34)
Histone	4	(12)
DNA topoisomerase 1 antibody,	3	(9)
Anti-neutrophil cytoplasmic antibody	2	(6)

Table 4 - Causes of mortality in children with systemic lupus erythematosus.

Patients number	AAP (years/gender)	DOD (years)	AAD (years)	Predisposing factors	Cause of death
1	6/M	13	19	SCD, grade IV MPGN, renal failure, HTN	Sickle cell disease and acute chest syndrome
2	6/M	12	17	Grade IV MPGN, poor compliance with treatment, renal failure, HTN	End stage renal disease, sepsis
3	11/M	2	13	Grade IV MPGN, poor compliance with treatment	Acute pulmonary embolism
4	13/F	3	16	Cardiomyopathy, persistent nephritis, renal failure	Multi -organ failure

AAP - age at presentation, DOD - duration of disease, AAD - age at the time of death, SCD - sickle cell Disease, HTN - hypertension, MPGN - membrano-proliferative glomerulonephritis

Table 5 - Frequencies of clinical and laboratory features of juvenile systemic lupus erythematosus in different ethnicities.

Involved organs	Present study (n=32 Bahraini)	Moradinejad et al[12] (n=45 Iranian)	Supavekin et al[13] (n=101 Thailander)	Bader-Meunier et al[9] (n=155 French)	Bahabri et al[14] (n=60 Saudi)
Mean age (years)	9±4	10.5±2.5	9.7±2.8	11.5±2.5	12.1
Female to male ratio	2.5:1	8:1	6.2 :1	4.5:1	5:1
Mucocutaneous (%)	93	88.8	76.3	70	81.6
Renal (%)	81	64.4	86.2	50	65
Musculoskeletal system (%)	65	77.7	31.7	64	91.6
Hematology (%)	56	55.5	73.4	72	66.6
Gastrointestinal tract (%)	31	-	19.8	16	-
Central nervous system (%)	31	17	20.8	17	30
Cardiovascular system (%)	21	26	13.9	15	38
Lungs (%)	21	11	6.9	15	16
ANA (%)	90.6	96	92	97	-
Anti ds DNA (%)	65	91	70.2	93	-

ANA - anti nuclear antibody, Anti ds DNA - anti double stranded DNA antibody

Table 6 - Prevalence of hemoglobinopathy and glucose-6-phosphate dehydrogenase deficiency in young Bahrainis and the study group.

Parameters	Bahrainis students[16]	Present study
No. of population	5685	32
Sickle cell trait (%)	13.8	6
Sickle cell disease (%)	1.2	18
Beta-thalasemia major (%)	0.09	3
G6PD deficiency (%)	23.2	15

G6PD - Glucose-6-phosphate dehydrogenase

Approximately 15-20% of cases of SLE occur in childhood, with a female to male ratio of 4.5:1, this ratio increases progressively to 9:1 by adulthood.[1,7,8] However in this study, the female to male ratio was 2.5:1, which indicates a higher male prevalence compared to previous reports.[9,10] This study also showed a lower prevalence of infantile onset of SLE. Only 2 patients (6.25%) had SLE <2 years of age. Incidence of infantile-onset of SLE was reported in 24% of 53 children with SLE and their main complications were cardiac and pulmonary.[11] However in this study infants with SLE showed no major organs involvement on their presentation. A comparison was made between this study finding and with other published reports as it was shown in **Table 5**. This study showed that male prevalence as well as the mucocutaneous manifestations was the most common organ involved in this study compared

to other studies. Prevalence of renal and hematological manifestations in this cohort and Iranian children who were reviewed by Moradinejad et al were comparable and the difference was statistically not significant (p=0.113 and 0.965).[12] When we compared our study with the study of Supavekin et al[13] the prevalence of renal manifestations was statistically significant (p<0.047) while the hematological manifestations was statistically not significant (p=0.063). In contrary, we reported more musculo-skeletal (MSK) abnormalities than Supavekin et al[13] study (p<0.001). When we compared the results findings of MSK and renal systems involvements to the study by Bader-Meunier et al[9] on French children, we reported almost similar prevalence of MSK symptoms (p=0.0914), however, the prevalence of renal manifestations was significantly higher in this study (p<0.001). Furthermore, the result of the study by Bahabri et al[14] on Saudi children showed higher prevalence of MSK symptoms among Saudi children (p<0.001) while the prevalence of renal manifestations were comparable (p=0.109). Prior et al[15] found that the first degree relatives of patients with SLE had a 4-fold risk of having autoimmune disease in comparison to first degree relatives of control. Systemic lupus erythematosus was reported significantly higher among the autoimmune diseases in the first-degree relatives. Eight patients in this research (25%) had relatives with SLE, 75% of them were first-degree relatives. When the prevalence of hemoglobinopathies and G6PD deficiency in young Bahrainis[16] was compared to the prevalence in this study group (**Table 6**), the result revealed no significant association of SLE and SCT in this study (p=0.219) while the co-existence of SLE and SCD was statistically significant (p<0.000). There were few studies showing the co-existence of SLE and SCD in children, suggesting that the association is rare.[17,18] However, high prevalence of SCD in our small cohort may carry its challenges in studying the genetic linkage between the 2 serious diseases. The overlap in the clinical pictures of SCD and SLE such as hemolytic anemia, arthritis, splenomegaly or hepatomegaly, makes the delay in diagnosing SLE for several months in most of these patients. The management of these patients is a challenge. There are no previous reported cases of coexisting beta thalassemia major and SLE. The incidence of nephritis in juveniles with SLE varies from 20-71%.[19,20] The renal manifestations in this study was comparable to the Saudi children as reported by Bahabri et al,[14] but significantly more than the French children as reported by Bader-Meunier et al.[9,14] Elevated levels of anti-DNA antibodies commonly precedes development of clinical lupus nephritis.[21] Seventy-six percent of patients with nephritis had a positive anti dsDNA antibody. Emre et al,[22] reported grade IV nephritis, as the most frequent histopathology (67.4%) among lupus nephritis in children. Among 15 children with renal biopsies, we reported grade IV nephritis in 9 (60%). Bogdanović et al,[23] showed that grade IV nephritis at initial biopsy is the only adverse effect on the lupus nephritis outcome. Grade IV MPGN was among the risk factors for death in 3 boys. Prevalence of CNS symptoms in this study was similar to the Saudi study (p=0.921) but higher than the French study (p=0.068).[9,14] Major cognitive disorders were reported in 3 patients in our study and also reported in other studies and most characteristic neuropsychiatric changes were observed in domains of memory, psychomotor speed and complex attention.[24,25] The CVS manifestations were reported in 38% of children in the Saudi study as compared to 21% in our study, (p=0.096) mainly in the form of cardiac and pulmonary manifestations. Libman-Sacks endocarditis was reported in 11% of patients with SLE in another study.[26] We reported a 9-year-old boy with endocarditis, mitral and aortic regurgitation. Cardiomyopathy is considered as unfavorable outcome in disseminated lupus erythematosus in children.[27] We identified a 16-year-old girl, who died with multi-organ failure due to uncontrolled cardiomyopathy. Prevalence of ANA level was comparable to that reported in other studies. In this study, nephritis was detected in 81% of patients with positive anti dsDNA antibody and in 81.8% among patients with negative anti dsDNA antibody. When Goodman and Kruskal tau test was used for correlation of positive anti dsDNA antibody with nephritis, result was not significant (p=0.95). Anticardiolipin antibodies (ACL) were requested for 13 patients only, it was positive in 6 patients only. Al-Saeid et al[10] reported ACL IgG in 37% and ACL IgM in 31% and contributed mainly to hematological problem, while our patients had different manifestations as previously discussed. Corticosteroid had been contributed to an increase prevalence of osteoporosis and considered as a risk factor for type 2 diabetes mellitus.[28,29] We reported osteoporosis in 2 patients and diabetes mellitus in one patient after prolonged administration of corticosteroid therapy. Life expectancy for children with SLE had significantly increased in the last 2 decades, however new type of morbidities arises because of the disease itself. Similar to other studies renal impairment was considered as a contributing factor to the morbidity of 4 patients in our study. [30]

The main limitations of this study was being a retrospective review, therefore studying the SLE activity by using SLE Disease Activity Index (SLEDAI) was difficult, as well as the wide variation in the follow-up observation years. Prospective study to measure SLEDAI at the beginning of the diagnosis and cumulative disease activity during the disease course is required.

SLE Disease Activity Index score can be correlated with the progression and the outcome of SLE after many years.[31]

In conclusions, the clinical and serological manifestations among children with SLE were comparable to those reported in other studies. Coexistence of SLE and SCD in 25% of our patients may herald further studies including genetic study to understand if there is any association between the two diseases or because of high prevalence of SCD among Bahraini population. Nephritis was reported in significant number of patients in this study and mainly contributed to their morbidity.

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