SLICC-based Phenotype of Juvenile Systemic Lupus Erythematosus in the Philippines

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ABSTRACT

Objective. To describe the clinical profile of Filipino pediatric SLE patients as determined using the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria.

Methods. We checked which among the SLICC criteria were fulfilled by Filipino pediatric SLE patients when we examined them and their case records, as part of a nationwide genetic study on SLE conducted from October 2015 to March 2017.

Results. Ninety-seven (out of 321) who were diagnosed to have SLE before 19 years of age were evaluated. The mean age of the population at the time of evaluation was 19.8 ± 6.9 years. Females comprised 94% of our population. Mean age of onset was 14.4 ± 2.7 years, while the mean age of diagnosis was at 14.5 ± 2.6 years. Acute cutaneous rash was found in 87%; oral ulcers 65%; renal disorder 63%; non-scarring alopecia 61%; arthritis 58%; chronic cutaneous rash 36%; leukopenia 35%; hemolytic anemia 34%; serositis 25%; thrombocytopenia 23%, and neurologic disorder 8%. Anti-nuclear antibody was present in 85%; low complement 32%; anti-dsDNA 28%; direct Coombs' 16%; antiphospholipid antibody 3%; and anti-Smith antibody 1%. Kidney biopsy was performed in only 14% (14/97) of patients, of whom 27% had class III histopathologic characteristic.

Conclusions. Filipino pediatric SLE patients typically present with mucocutaneous, renal, and musculoskeletal involvement. Cardiopulmonary and neurologic manifestations are found to be less common among them. Finally, renal biopsy is not commonly performed among these patients.

Key Words: Systemic lupus erythematosus; children; Philippines; SLICC

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex prototypic autoimmune disease commonly affecting women at their child-bearing age at a prevalence of 20 to 150 per 100,000. In Asia, prevalence data generally fall within 30-50 per 100,000 population[1], a rate higher than the 25/100,000 reported in UK[2]. Twenty percent of SLE patients have disease onset during childhood and adolescence. It has a global incidence of 0.36-2.5 per 100,000 and prevalence rate of 1.89 to 25.7 per 100,000 children.[3] This report describes the clinical and immunologic profile of childhood-onset SLE patients enrolled in the first nationwide SLE Genetics Study in the Philippines using the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria.

PATIENTS AND METHODS

This report is part of the research program of the UP Manila Genetics of SLE Study Group done during the

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period of October 2015 to March 2017. All procedures have been reviewed and approved in compliance with the ethical standards of the National Institutes of Health, University of the Philippines Manila-Research Ethics Board and the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects. All participants signed the informed consent and/or assent forms.

We recruited volunteer participants diagnosed with SLE who satisfy the 2012 SLICC classification criteria from rheumatology clinics in both private and government institutions, including the Philippine General Hospital, University of the Philippines Manila, communities in Metro Manila, Baguio, Nueva Ecija, Batangas, Cebu, and Iloilo. Trained research staff gathered relevant demographic and health information by interview using the standardized forms. Available medical records were reviewed as cross-reference for the diagnosis of SLE. We excluded patients with co-existing autoimmune diseases like rheumatoid arthritis, juvenile idiopathic arthritis, systemic vasculitides, dermatomyositis, scleroderma, mixed connective tissue disease, and overlap syndromes. We also obtained relevant laboratory information from the subject's medical record. No new diagnostic procedures were performed. Patients who were diagnosed to have SLE prior to their 19th birthday were evaluated.

RESULTS

There were ninety-seven patients with juvenile SLE (jSLE) out of the 321 recruited in the Genetics of SLE Study. There were 91 females and 6 males at 15:1 ratio. The mean age of onset of symptoms was 14.4 ± 2.7 years (range, 7-18 years) and the mean age of SLE diagnosis was 14.5 ± 2.6 years (range, 7-18 years).

The frequency of the different clinical and immunologic manifestations based on the SLICC criteria is shown on Table 1. The common clinical manifestations of jSLE were acute cutaneous rash (87%), oral ulcers (65%), renal disorder (63%), non-scarring alopecia (61%), and arthritis (58%). Hematologic manifestations of hemolytic anemia, leukopenia, and thrombocytopenia were found in 34%, 35%, and 23% of patients, respectively. Serositis was present in 25% and neurologic disorder in 8%. While not all immunologic tests were done on all participants, antinuclear antibody was found in the majority at 88%. Low complement level was seen in 33%, positive anti-dsDNA in 29%, direct Coombs' test in 16%, antiphospholipid antibody in 3%, and anti-Smith antibody in 1% of the patients. Kidney biopsy was performed in only 14% of patients, of whom 29% had focal proliferative glomerulonephritis (WHO Class III), followed by 21% each of mesangioproliferative (Class II), and diffuse proliferative glomerulonephritis (Class IV) and membranous nephropathy (Class V) in 7%. No report was seen on the other 21% of patients.

Table 1. Demographic profile and SLE manifestations based on SLICC criteria

Variable	SLE N=97
Age (years, mean ± SD)	19.8 ± 6.9
Age at symptom onset (years, mean ± SD)	14.4 ± 2.7
Age at diagnosis (years, mean ± SD)	14.5 ±2.6
Female sex, frequency (%)	91 (94%)
SLE manifestations, frequency (%)	
Acute cutaneous lupus	84 (88%)
Chronic cutaneous lupus	35 (36%)
Oral or nasal ulcers	63 (65%)
Non-scarring alopecia	59 (61%)
Arthritis	56 (58%)
Serositis	24 (25%)
Renal	61 (63%)
Neurologic	8 (8%)
Leukopenia	34 (35%)
Hemolytic anemia	33 (34%)
Thrombocytopenia	22 (23%)
SLE laboratory manifestations, frequency (%)	
ANA	85 (88%)
Anti-dsDNA	28 (29%)
Low complement	32 (33%)
Kidney biopsy	14 (14%)
Direct Coombs' test	16 (16%)
Anti-Sm	1 (1%)
Antiphospholipid antibody	3 (3%)

Note: SLICC – Systemic Lupus International Collaborating Clinics

DISCUSSION

In this first multi-center and multi-regional report in the Philippines, we used the 2012 SLICC SLE classification criteria in describing the main clinical and laboratory manifestations of juvenile SLE. The SLICC criteria was found to be more sensitive (99.9% vs. 84.3%) but less specific (82.0% vs. 94.1%) than the ACR criteria.[4] In a local validation study among juvenile SLE patients, the sensitivity was 94.0% (95%CI 88.9-97.2) and the specificity was 96.7% (95%CI 92.4-98.9).[5] The higher specificity of the SLICC criteria leads to fewer misclassifications, making it better criteria for observational and clinical trial studies.[6,7] In considering our results, we cited international studies as seen in Table 2. However, these cited papers used the revised 1997 ACR criteria[8-18] or the modified American Rheumatism Association criteria for SLE[10,19]. Only our study used the SLICC criteria. We included representative studies from the different regions of the world. Southeast Asia is represented by the countries Malaysia[9], Singapore[10], Vietnam[11], and another local study from the Philippines[8]. Bangladesh[12] and India[19] represented South Asia, China[13] of the East Asia and Iran[14] of the Middle East. Other populations are from the continent of Australia[15] through its Australian Paediatric Surveillance Unit, nine countries from Latin America[16] obtained from the GLADEL (Grupo Latino Americano de Estudio del Lupus) database, Canada[17] and four countries from Europe[18] which were composed of 80% Caucasians.

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Table 2. Comparison of the main clinical and laboratory features of jSLE patients from our study and other international studies

	Our study 2019	[a] Gulay[7] 2011	[a] Ilias[8] 2017	Tan[9] 2015	Dung[10] 2012	[a] Rahman[11] 2014	[a] Agarwal[18] 2009	[a] Feng[12] 2013	[a] Fatemi[13] 2016	[a] Mackie[14] 2015	Ramirez Gomez[15] 2008	Hiraki[16] 2008	Hoffman[17] 2009
Country	Philippines	Philippines	Malaysia	Singapore	Vietnam	Bangladesh	India	China	Iran	Australia	Latin America [b]	Canada	Europe [c]
Number	97	78	51	64	45	70	70	259	180	30	230	256	56
Female:Male ratio	15:1	10:1	10:1	5:1	4:1	7:1	6:1	16:1	3.3:1	4:1	9:1	4.7:1	5:1
Age at diagnosis (years, mean ± SD)	14.5 ± 2.6	14 ± 2.7	12[d]	11.9	12.8 ± 2.5	11.6 ± 2.6	10.5	NS	NS	12.6[d]	16.4	13.1 ± 3.2	15
Mucocutaneous (%)	NS	92.3	NS	62.5	NS	NS	NS	78	NS	NS	NS	NS	NS
Acute rash (%)	87	76.9	52	45.3	67	71	57.1	NS	49	47	70.4	66	69.6
Chronic rash (%)	36	35.8	18	15.6	13	NS	NS	NS	NS	10	12.6	43	13.2
Photosensitivity	NS	73	20	15.6	53	59	51.4	NS	NS	31	53	20	44.6
Oral ulcers (%)	65	67.9	40	32.8	38	73	NS	NS	10	17	49.1	30	28.6
Alopecia (%)	61	52.5	24	42.2	NS	51	45.7	NS	NS	NS	NS	29	41.1
Musculoskeletal (%)	58	53.8	44	56.3	58	74	65.7	49.8	50.5	76	83	67	59.3
Serositis (%)	25	21.7	28	7.8	36	10	2.8	23.2	5	14	17.4	15	18.5
Renal (%)	63	71.7	60	50	82	66	77.1	53.2	72.8	27	49.1	55	62.5
Neurologic (%)	8	32	9	12.5	16	26	21.4	5.4	11.7	3	11.3	27	20.4
Hematologic (%)	NS	69.2	60	NS	78	NS	NS	68	NS	77	NS	NS	NS
Hemolytic anemia (%)	34	10.2	NS	28.1	NS	16	60	43	12.2	40	16.4	25	38.5
Leukopenia (%)	35	32	6.1	67.2	NS	10	NS	38.4	11.1	40	46.1	36	63.6
Lymphopenia (%)	NS	41	NS	90.6	NS	NS	NS	NS	NS	60	60.4	NS	67.9
Thrombocytopenia (%)	23	25.6	4.1	32.8	NS	17	24.2	28.9	15	17	25.2	31	31.5
ANA (%)	85	98.5	98	98.4	67	97	NS	95.7	97.2	100	96.9	100	NS
Anti-dsDNA (%)	28	NS	34.7	90.6	95	91	77.1	57.8	85.5	86.7	67	84	NS
Anti-Sm (%)	1	NS	NS	37.5	NS	NS	NS	30.7	NS	26.7	51.3	48	60.7
Antiphospholipid antibody (%)	3	NS	NS	NS	NS	9	NS	NS	2.2	33	NS	45	17.9
Low complement (%)	32	8.9	83.3	NS	NS	83	80	NS	11.1	NS	NS	NS	NS
Coombs' test (%)	16	NS	70.6	NS	12	NS	58.3	NS	NS	NS	NS	25	NS
Kidney Biopsy (%)	14	30.8	49	32.8	64	60	100	NS	13.9	36.7	NS	55	NS

Abbreviations: NS = Not specified, ANA = antinuclear antibody
[a] At diagnosis; [b] included Mexico, Brazil, Argentina, Colombia, Venezuela, Chile, Peru, Cuba and Guatemala;
[c] included Belgium, the Netherlands, Slovakia and UK; [d] median age

As expected, girls are more frequently affected than boys but our report had the highest ratio at 15:1 comparable to the China[13] cohort of 16:1. The female to male ratio in other countries ranged from 3 to 10:1.[9-12, 14-19] The mean age of diagnosis of 14.5 ± 2.6 years is well within the reported range except those from Vietnam, Bangladesh, Australia, and India which may be due to their cut-off age for jSLE of either below 15 or 16 years.[11,12,15,19]

Mucocutaneous involvement is the most commonly affected system in our report similar to the local study of Gulay and Dans on jSLE patients in the biggest tertiary hospital in Manila.[8] A high frequency of involvement of sixty to seventy percent is also seen among children in majority of Southeast Asian countries, China, Latin America, Canada, and Europe with acute cutaneous lupus or malar rash as the most common presentation. Oral ulcers and alopecia are more frequent than chronic cutaneous rash among Filipinos. Musculoskeletal involvement seen in our cohort of jSLE is similar with the other countries, but is more frequently reported in Bangladesh, Latin America, and Australia.

Lupus nephritis is one the most severe clinical manifestation of SLE associated with higher morbidity and mortality. It is more frequently a presenting manifestation among pediatric rather than adult-onset SLE.[20] In our comparative table, sixty to eighty percent of children with lupus are afflicted in the countries of Vietnam, India, Iran, Philippines, Bangladesh, Malaysia, and those in the continent of Europe. While our cohort had focal lupus nephritis (WHO Class III) with the highest proportion at 29%, diffuse proliferative lupus nephritis (WHO Class IV) is the most common histopathologic finding among those who had kidney biopsy in other populations. The report of lupus nephritis is lowest in Australia (27%).

While hematologic disorder is less common in our study at about one-third, it is common to our neighboring Asia Pacific countries of Singapore, Vietnam, and Australia with more than three-fourths of their cohort involved.

Cardiopulmonary and neurologic disorders are infrequent in the pediatric age group as compared to other organ involvement. We report occurrence of serositis in a quarter of our jSLE patients. It is more frequent in Vietnam (36%) but less common in Singapore, India, and Iran (<10%). Neurologic involvement is our least frequent manifestation at 8%.

The frequency of ANA positivity in our study (85%) is lower than the other studies (95-100%); even lower is among the Vietnamese children at 67%. While not all our patients had complete antibody profile, the more frequent immunologic tests done were ANA, complement, and anti-dsDNA levels.

The report is limited with the small sample size with data collected from the various private and public rheumatology clinics in the Philippines. Consequently, there may be selection bias in the patient participation. It is an accepted fact that we are confronted with survival bias as patients with more severe manifestations at the onset may have succumbed to serious complications of lupus flare.

CONCLUSION

Filipino pediatric SLE patients typically present with mucocutaneous, renal, and musculoskeletal involvement. Cardiopulmonary and neurologic manifestations are found to be less common among them. Finally, renal biopsy is not commonly performed among these patients.

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Statement of Authorship

Both authors participated in data collection and analysis, and approved the final version submitted.

Author Disclosure

Both authors declared no conflicts of interest.

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