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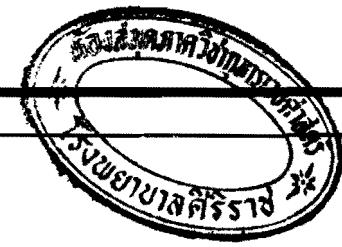

Age-Related Differences on Clinical and Immunological Manifestations of SLE

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SUMMARY **The clinical and immunological manifestations of 51 children with onset of systemic lupus erythematosus (SLE) before the age of 15 were compared with those of 308 adult patients with disease onset between the age of 15-49 and another 27 elderly lupus patients whose disease onset occurred at or after the age of 50. Overall disease activity determined by mean SLEDAI score was highest in the childhood group followed by the adult and the elderly group respectively. More severe form of cutaneous involvement, adenopathy, hypertension, renal involvement with renal insufficiency and anti-nDNA antibodies occurred predominantly in the childhood lupus. The clinical features distinguishing old-age lupus were chronic disease with a long interval between the time of onset and diagnosis, higher incidence of discoid rash and lower incidence of malar rash and renal involvement. Frequencies of anti-nDNA antibodies and renal involvement gradually decreased from childhood, to adulthood and to elderly lupus respectively. Anti-Sm antibodies were predominant in the adult onset group. Genetic markers, sex hormones and senility of the immune system may play a role in these age-related diferences in clinical and immunological manifestations in SLE.**

Attempts to study causative factors and understand immunopathogenic mechanisms in systemic lupus erythematosus (SLE) have been hampered by the diversity of clinical manifestations of this illness. To circumvent this problem, the investigation of more homogeneous subgroups of patients has been advocated.[1] While numerous studies have described age as a factor associated with the clinical heterogeniety of SLE,[2] most of these studies focused on lupus in the older age group. The purpose of our study was to clarify the relationship between age and the clinical and serological abnormalities of SLE by comparing the differences in manifestations among childhood, adult and the elderly lupus patient groups.

PATIENTS AND METHODS

Three hundred and eighty-six patients have been diagnosed as SLE at Ramathibodi hospital, Bangkok, Thailand during a 3 year period (1990-1992). All met the American Rheumatism Association revised criteria for SLE.[3] No patient had a history of exposure to drugs believed to produce the SLE syndrome.[4] In 51, the onset of disease (defined as the first manifestation characteristic of lupus) occurred before the age of 15, and they represent childhood lupus described in this report. The 308 adult lupus had their onset of disease at age between 15-49. The remaining 27 patients, representing elderly lupus, had their disease onset after the age of 50. A detailed clinical and laboratory assessment at their initial presentation was made according to a formalized data sheet.

In examining the spectrum of the disease, the occurrence of 13 major clinical features and 18 laboratory and immunological findings were recorded. The clinical manifestations included: 1) fever > 38°C; 2) cutaneous involvement; 3) mus-

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culoarticular manifestations (arthalgia, arthritis, myalgia and myositis); 4) pleuropericarditis; 5) lymphadenopathy; 6) Raynaud's phenomenon; 7) neuropsychiatric manifestations (seizure, psychosis, or objective neurologic findings in the absence of another definable cause); 8) renal involvement meeting ARA criteria;[3] 9) hematologic involvement according to ARA criteria;[3] 10) pulmonary involvement (atelectasis, pneumonitis, interstitial fibrosis, pulmonary hypertension); 11) gastrointestinal (GI) involvement (unexplained abdominal pain, inflammatory bowel, pancreatitis, hepatitis, peritonitis); 12) cardiac involvement (unexplained cardiac murmur, arrhythmia, cardiomegaly); 13) hypertension.

The laboratory and immunological presentations were recorded as occurrence of : 1) anemia (hematocrit < 30%), 2) leukopenia (leukocytes < 4,000/mm^3); 3) thrombocytopenia (platelets < 100,000/mm^3); 4) elevated erythrocyte sedimentation rate (ESR > 30 mm/hr Westergren); 5) positive direct Coomb's test; 6) proteinuria (≥ 500 mg/24 hours); 7) hematuria (> 5 RBC/HPF); 8) cellular casts; 9) unexplained elevation of serum creatinine (≥2 mg/dl); 10) positive LE cell preparation; 11) depressed serum total hemolytic complement (CH_{50}) levels; 12) positive fluorescent antinuclear antibody test using mouse kidney as substrate (titre ≥ 1:16 for speckle pattern[5]); 13) anti-nDNA antibodies as detected by the crithidea luciliae immunofluorescent method.[6] Precipitating antibodies to soluble nuclear and cytoplasmic antigens including: 14) anti-Sm antibodies; 15) anti-RNP antibodies; 16) anti-SSB antibodies and 17) anti SSA antibodies were detected by double immunodiffusion in Ouchterlony plates containing 0.4% agarose.[7] Active extracts of rabbit thymus acetone powder (RTE) were supplied by Pel-Freeze Biologicals, Rogers, Arkansas while human spleen extracts (HSE) were prepared as described in previous report.[8] Prototype sera were kindly supplied by the University of Colorado Health Science Center ANA laboratory, Denver, Colorado. Lastly : 18) anticardiolipin antibodies (ACA) were measured by an enzyme linked immunosorbent assay according to the procedure described by Harris EN, *et al.*[9] Results were expressed as a binding index (BI) calculated from the ratio of the optical density (OD) value of patients' sample to that of pooled normal.[10] A positive value is defined as a BI more than 3 standard deviations above the mean normal control values of the 100 normal subjects.

Overall disease activity at the time of diagnosis of patients in each lupus subgroups was assessed by the SLE disease activity index (SLEDAI).[11] This measurement consists of weighted scores for the presence of specific clinical features and laboratory findings. Items that are life-threatening have higher weights. Total overall score is calculated by summing the predetermined weights for the items that are present. This index was developed with a panel of experienced rheumatologists with expertise in SLE and is useful in comparing groups of patients in terms of disease activity and not just the presence of organ involvement. The evaluation of this index in our patients was performed by the same staff rheumatologist at the time of chart review.

Fisher's exact test and Chi-square test were used for statistical analysis. Significance level was set at $p < 0.05$.

RESULTS

Of 386 SLE patients being diagnosed at Ramathibodi hospital in the period 1990-1992, 51 patients (13.2%) were in the childhood group; 308 patients (79.8%) were in the adult group and 27 patients (6.99%) were in the elderly group. Their mean ages at onset were 11 (range 3-14), 28 (range 15-49) and 54 (range 50-62) years old respectively. The interval from the time of onset until diagnosis of lupus in the elderly group was significantly longer than the childhood group ($p = 0.0028$). However, we found marked variation in these intervals i.e., the intervals ranged from 1-96 months in

Table 1. Characteristics of 386 lupus patients and their overall disease activity at time of diagnosis.

	Childhood	Adult	Elderly
Number of patients (%)	51 (13.2)	308 (79.8)	27 (6.99)
Mean age at onset (years)	11	28	54
Range (years)	3-14	15-49	50-62
Mean interval from onset to diagnosis (months)*	4.2 ±6.5	8.4 ±13.8	17.7 ±27.1
Female/Male	6.3/1	9.3/1	5.8/1
Mean SLEDAI score $	18.3 ±7.9	15.3 ±8.9	13.7 ±5.9

*p=0.0028 childhood vs elderly

$p=0.023 childhood vs adult, p=0.0084 childhood vs elderly

the elderly group, to 1-72 months in the adult group and 1-36 months in the childhood group. The female to male ratio decreased from 9.3/1 in adult lupus to 6.3/1 in the pediatric subgroup and 5.8/1 in the elderly. Overall disease activity determined by mean SLEDAI score was significantly more severe in the childhood lupus group than in the adult ($p = 0.023$) and the elderly lupus groups ($p = 0.0084$) as shown in Table 1.

Comparison of clinical presentations are demonstrated in Tables 2 and 3. Although all three groups had comparable frequencies of cutaneous involvement, they had different modes of presentation (Table 2). Chronic discoid lesion was particularly a disease of the elderly as its frequency significantly increased with age from 3.9% in children to 19.2% in adults ($p = 0.01$) and up to 37% in the elderly ($p = 0.04$, adult vs elderly). The older onset group developed malar rash (25.9%) less frequently than the adult (62%, $p = 0.0006$) and the pediatric lupus groups (58.8%, $p = 0.013$). While childhood lupus more commonly manifested vasculitis than the adult group (19.6% vs 3.9%, $p = 0.0004$), they less frequently showed photosensitivity (15.9% vs 41.8%, $p = 0.0017$) and Raynaud's phenomena (2% vs 15.6%, $p = 0.03$). Adenopathy was also more prominent in children than in the adult onset group (27.4% of other organ manifestations were comparable among the three groups except for renal involvement and hypertension which occurred most commonly in children (Table 3). Incidence of clinical renal disease decreased with age from 82.4% in children to 66.9% in adults ($p = 0.06$) and 44.4% in the elderly ($p = 0.003$) childhood vs elderly, $p = 0.03$ adult vs elderly). Hypertension was found in 13.7% of childhood lupus compared to 3.9% in adults ($p = 0.02$) and 3.7% in late onset lupus ($p = 0.034$).

Table 2. Comparison of minor clinical presentations in lupus patients with different age at onset.

Manifestations	Childhood N=51 (%)	Adult N=308 (%)	Elderly N=27 (%)	p
Fever 38°c	24 (47.7)	116 (37.7)	12 (44.4)	NS
Cutaneous	34 (66.7)	207 (67.2)	18 (66.7)	NS
malar rash	30 (58.8)	191 (62.0)	7 (25.9)	*
photosensitivity	8 (15.9)	129 (41.8)	8 (29.6)	**
oral ulcer	18 (35.3)	89 (28.9)	8 (29.6)	NS
discoid rash	2 (3.9)	59 (19.2)	10 (37.0)	$
vasculitis	10 (19.6)	12 (3.9)	3 (11.1)	+
Raynaud's	1 (2.0)	48 (15.6)	2 (7.4)	#
Musculoarticular	26 (50.9)	185 (60.1)	21 (77.8)	NS
Pleuropericarditis	7 (13.7)	37 (12.0)	4 (14.8)	NS
Adenopathy	14 (27.4)	18 (5.8)	3 (11.1)	++

*p=0.013 childhood vs elderly, p=0.0006 adult vs elderly
**p=0.0017 childhood vs adult
$p=0.01 childhood vs adult, p=0.0003 childhood vs elderly and p=0.04 adult vs elderly
+p=0.0004 childhood vs adult
#p=0.03 childhood vs adult
++p=0.00002 childhood vs adult

Table 3. Comparison of major organ manifestations in lupus patients with different age at onset.

Manifestations	Childhood N=51 (%)	Adult N=308 (%)	Elderly N=27 (%)	p
Neuropsychiatric	9 (17.6)	49 (15.9)	6 (22.2)	NS
Renal	42 (82.4)	206 (66.9)	12 (44.4)	*
Hematologic	24 (47.1)	188 (61.0)	16 (59.3)	NS
Pulmonary	8 (15.7)	68 (22.1)	5 (18.5)	NS
Gastrointestinal	7 (13.7)	31 (10.1)	2 (7.4)	NS
Cardiac	5 (9.8)	46 (14.9)	3 (11.1)	NS
Hypertension	7 (13.7)	12 (3.9)	1 (3.7)	$

*p=0.06 childhood vs adult, p=0.003 childhood vs elderly and p=0.03 adult vs elderly
$p=0.02 childhood vs adult, p=0.034 childhood vs elderly

Table 4. Comparison of laboratory manifestations in lupus patients with different age at onset.

	Childhood N=51 (%)	Adult N=308 (%)	Elderly N=27 (%)	p
Anemia	31 (60.7)	127 (41.2)	13 (48.1)	NS
Leukopenia	61 (11.8)	79 (25.6)	9 (33.3)	NS
Thrombocytopenia	5 (9.8)	25 (8.1)	4 (14.8)	NS
ESR 30 mm/hr	45 (88.2)	284 (92.3)	25 (92.6)	NS
Proteinuria	36 (70.6)	206 (66.9)	12 (44.4)	*
Hematuria	35 (68.6)	144 (46.8)	7 (25.9)	$
Cellular casts	20 (39.2)	73 (23.7)	4 (14.8)	+
Cr 2 mg/dl	12 (23.5)	33 (10.7)	2 (7.4)	#

*p=0.054 childhood vs elderly, p=0.03 adult vs elderly
$p=0.0125 childhood vs adult, p=0.0596 adult vs elderly and p=0.0013 childhood vs elderly
+p=0.0524 childhood vs adult, p=0.0285 childhood vs elderly
#p=0.02 childhood vs adult, p=0.068 childhood vs elderly

Table 5. Comparison of immunologic manifestations in lupus patients with different age at onset.

	Childhood N=51 (%)	Adult N=308 (%)	Elderly N=27 (%)	p
Direct Coomb's test	24 (47.1)	167 (54.2)	13 (48.1)	NS
LE cells	18 (35.3)	99 (32.1)	6 (22.2)	NS
ANA	51 (100.0)	305 (99.0)	26 (96.3)	NS
Depressed CH_{50}	41 (80.5)	233 (75.6)	25 (92.6)	NS
Anti-nDNA	38 (74.5)	164 (53.2)	7 (25.9)	*
Anti-Sm	15 (29.4)	133 (43.2)	5 (18.5)	$
Anti-RNP	17 (33.3)	142 (46.1)	9 (33.3)	NS
Anti-SSA	16 (31.4)	118 (38.3)	10 (37.0)	NS
Anti-SSB	2 (3.9)	25 (8.1)	3 (11.1)	NS
Anticardiolipin	24 (47.1)	107 (34.7)	11 (40.7)	NS

*p=0.015 childhood vs adult, p=0.0002 childhood vs elderly and p=0.013 adult vs elderly
$p=0.02 adult vs elderly

As shown in Table 4, pediatric lupus more commonly manifested abnormal urine sediments and high serum creatinine than their older counterparts. Table 5 compares the immunologic abnormalities in lupus with different age at onset. They had similar patterns of abnormal serological manifestations. However the incidence of anti-nDNA antibodies significantly decreased with age from 74.5% in children to 53.2% in adults (p=0.015) and 25.9% in the elderly (p=0.013 adult vs elderly). Anti-Sm antibodies were significantly more prominent in the adult (43.2%) than the elderly lupus group (18.5%, p=0.02). There was no statistical significant difference in the incidences of anti-RNP, anti-SSA, anti-SSB, and anticardiolipin antibodies among the three groups.

DISCUSSION

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder of unknown etiology which exhibits a wide spectrum of both clinical and immunological features. The disease is most prevalent among peoples in their 20s or 30s. However it can affect any persons from infancy to old age. The purpose of the present study is to assess the utility of a readily determined value, age at disease onset, as a discriminator of clinical and serological disease expression.

As previously known, our study demonstrated that most lupus patients were first diagnosed in the 15 to 49 years age group (79.8%). The incidence of SLE in children (13.2%) was two times more common than in the elderly (6.99%). The adult onset group revealed a marked female predominance in comparison to the childhood and the elderly groups. These age-related differences in the ratio of sex-specific incidence may be the result of hormonal changes occurring during puberty and the childbearing years.

Age also showed some relationship with the pattern of clinical involvement. Childhood patients with SLE appeared to have the most severe disease. They scored more on the overall disease activity index or SLEDAI. This index takes into account the number of disease activity descriptors involved in each organ system in patients with SLE. So it represents global indices of activity in SLE and can serve better than the degree of involvement of a single organ or serologic activity in comparing series of patients in term of disease activity and not just the presence of organ involvement. Although the SLEDAI has not yet been fully validated for use as a prognostic device, the result of a preliminary study indicates that it is a strong predictor of mortality in SLE.[12] Interestingly, a trend towards most severe disease in children was also reflected in cutaneous presentations. Vasculitis which bears the worst prognosis among various forms of skin involvement in SLE was found in highest percentage in the childhood onset whereas discoid lupus, which runs a chronic benign course, was most prominent in elderly lupus. Adenopathy, hypertension and high serum creatinine level were all manifested by childhood lupus in higher frequencies than by the other two groups.

Raynaud's phenomenon occurred predominantly in the adult onset lupus. Anti-nRNP which was found to be associated with Raynaud's phenomenon[13] also revealed a tendency to be more frequent in adult onset patients but with no statistically significant difference. Ward *et al*[14] reported that patients with high titres of anti-nDNA antibodies were at increased risk for lupus nephritis. Our study also demonstrated that the incidence of renal involvement and anti-nDNA antibodies gradually decreased between the pediatric, adult and older onset patients, respectively. Although adult lupus patients were more likely to have anti-Sm antibodies than the other groups, we found no clinical correlation with this type of antibody.There were no statistical significant differences between the three groups in the incidence of hypocomplementemia, anti-SSA, anti-SSB, and anticardiolipin antibodies.

In conclusion, our study demonstrated age-related changes in disease manifestations. The differences in the clinical expression appeared to be correlated with some immunological abnormalities. Age may affect the clinical and immunological manifestations of SLE through the changing level of sex hormones and senility of the immune system, while genetic factors may determine the age at which SLE will manifest.

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