Original Article

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Pathology Section

Autoantibody Profile of Childhood Onset Systemic Lupus Erythematosus: An Audit of Immunopathology Laboratory of a Tertiary Care Centre, Varanasi, India

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ABSTRACT

Introduction: Systemic Lupus Erythematous (SLE) is an autoimmune disease, which commonly affects females and is associated with formation of various Antinuclear Antibodies (ANA). Childhood onset SLE has some similarities and differences in immunological profile and clinical manifestations from adult onset SLE patients.

Aim: To study the spectrum of clinical manifestation and autoantibody profile of childhood onset SLE patients and to compare with adult SLE patients.

Materials and Methods: This was a retrospective observational study conducted from October 2017 to March 2021 in Department of Immunopathology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. This includes 74 patients of childhood onset SLE and 91 patients of adult SLE. Detailed clinical and laboratory data were collected from medical records. Serum ANA and anti-dsDNA (Deoxyribonucleic Acid) detection was done by solid phase enzyme immunoassay methods. Antibodies to extractable nuclear antigen were detected by dot blot immunoassay. Chi-square test {International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 21.0} was used to compare categorical data of childhood onset SLE and adult SLE patient groups.

Results: The mean age of childhood onset SLE patients was 13.05±4.26 years with female:male ratio of 3.93:1. Malar rash (p=0.001) and renal involvement (p=0.021) was significantly more frequent in childhood onset SLE but oral ulcer was significantly more frequent (p=0.038) in adult patients. Anti-ds DNA positivity and reduction in complements C3 and C4 were more commonly seen in childhood onset SLE patients.

Conclusion: Age is an important influence on clinical manifestations and autoantibody profile of SLE. Childhood onset SLE showed more frequent renal and skin involvement and more significant activity measured by reduction of complements. Awareness of the same will help our clinicians to detect renal involvement at an early stage and develop organ specific management protocol.

Keywords: Age of onset, Autoantibodies, Lupus nephritis, Paediatric lupus

INTRODUCTION

The SLE is an autoimmune disease associated with the involvement of multiple organs like kidneys, skin, Central Nervous System (CNS) and musculoskeletal system. Various ANA are elevated in patients of SLE. These antibodies play an important role in the pathogenesis and diagnosis of SLE. Young females of reproductive age group are commonly affected in SLE. Paediatric onset SLE accounts for about 10-20% of all SLE cases. The incidence of SLE is 0.3-0.9 per 100,000 children per year and the prevalence of SLE is 3.3-24 per 100,000 children [1]. When SLE first appears in an individual less than 18 years of age, it is commonly referred as childhood onset SLE [2]. Previous meta-analysis studies reveal presence of differences in clinical presentation and ANA profile between childhood onset SLE patients and adult SLE patients [3,4].

There are very limited studies on the antibody profile of childhood onset SLE patients and its clinical significance, in Indian population [5-10]. The objective of the present study was to evaluate the spectrum of clinical manifestations and autoantibody profile of childhood onset SLE patients and to compare it with adult SLE patients. The differences between childhood and adult SLE if found significant, can alert the paediatric physician in early detection of complications and initiation of treatment.

MATERIALS AND METHODS

The present study was a retrospective observational study conducted at University Grants Commission (UGC) Advanced Immunodiagnostic Training and Research Centre of a tertiary care teaching institution of Banaras Hindu University, Varanasi, Uttar Pradesh, India from October 2017 to March 2021. Data analysis was done between April 2021 to June 2021. Ethical approval from Institutional Ethics Committee (IEC) was taken (No. Dean/2021/EC/2800).

Inclusion criteria: Newly diagnosed SLE patients, diagnosed by the revised 1997 American College of Rheumatology (ACR) criteria and Systemic Lupus International Collaborating Clinics classification criteria (SLICC, 2012) were included [11]. For childhood onset SLE, the age of patients was below 18 years, and above 18 years patients were included in adult SLE.

Exclusion criteria: Pretreated cases of SLE were excluded as treatment can alter the autoantibody profile and clinical manifestations.

A total of 74 SLE cases of children and 91 adult SLE cases diagnosed at our centre were included. Sample size was calculated by using online software www.openepi.com.

Detailed clinical, demographic and laboratory data were collected from medical records. Renal involvement of SLE was defined by presence of one of the following ACR criteria:

1-persistent proteinuria greater than 500 mg per 24 hours;

2-presence of cellular cast, and

3-biopsy proven lupus nephritis [11].

Serum ANA detection was done by solid phase enzyme immunoassay ANA kit (AESKU. diagnostic, Germany). Serum level of anti-dsDNA was measured by quantitative solid phase enzyme immunoassay dsDNA kit (AESKU. diagnostic, Germany). Serum level of anti-dsDNA

more than 24 IU/mL was considered positive. Anti-Smith (Sm), anti-Sjögren's-Syndrome-related antigen A (SS-A), Anti-Sjögren's-Syndrome-related Antigen B (SS-B), Anti-U1 Ribonucleoprotein (RNP), anti-centromere, anti-Jo-1 anti-Scleroderma (Scl)-70 antibodies were detected by dot blot immunoassay kit (D-tek, BlueDot ANA8 IgG kit, Belgium). Serum complement C3 and C4 was measured by Nephelometer (Immage 800 protein chemistry analyser, Beckman Coulter, USA). Serum samples were stored at -80°C. The clinical presentation, autoantibody profile and serum complement level of childhood onset SLE patients and adult SLE patients were compared.

STATISTICAL ANALYSIS

Statistical analysis was performed by Statistical Package for the Social Sciences (SPSS) version 21.0. Quantitative variables were expressed as mean and Standard Deviation (SD). Categorical variables were expressed as frequency. Chi-square test was used to compare categorical data of childhood onset SLE and adult SLE cases. The p-value <0.05 was considered as statistically significant.

RESULTS

Among total 74 patients of childhood onset SLE, 59 (79.73%) were females and 15 (20.27%) were males with female:male ratio of 3.93:1. The mean age of childhood onset SLE patients was 13.05±4.26 years. The youngest patient was 1.5 years of age. Nine patients (12.16%) belonged to less than 5-years age group and 14 (18.92%) patients were present in 5-12 years age group. Majority of the patients 51 (68.92%) were in 12-18 years age group.

Out of 91 adult SLE cases, 76 (83.52%) were females and 15 (16.48%) were males. Female:male ratio in adult SLE cases was 5:1. Mean age of presentation in adult patients was 33.49±7.33 years. Arthritis was the most common clinical presentation in both childhood (81.08%) and adult (89.01%) SLE patients. Malar rash was next most common clinical manifestation in paediatric patients, however, haematological abnormalities were second most frequent manifestation in adult SLE patients. Malar rash, nephritis, pericarditis, fever and neuropsychiatric symptoms were more common in childhood onset SLE patients group as compared to adult patients. But only malar rash (p=0.001) and nephritis (p=0.021) were significantly more frequent in childhood onset patients. Oral ulcer was significantly more frequent (p=0.038) in adult patients. Arthritis, discoid rash, pleuritis, haematological abnormalities, photophobia were more common in adult cases but did not show significant difference [Table/Fig-1]. Anaemia was the most common haematological abnormalities detected in 40 (54.05%) patients of childhood onset SLE. Distribution of various haematological manifestations in childhood SLE patients and adult SLE patients are shown in [Table/Fig-2].

Parameters	Childhood onset SLE group (n=74), Number (%)	Adult SLE group (n=91) Number (%)	χ^2	p-value
Malar rash	48 (64.86)	36 (39.56)	10.450	0.001*
Discoid rash	13 (17.56)	18 (19.78)	0.131	0.717
Alopecia	35 (47.29)	56 (61.53)	3.346	0.067
Oral ulcer	18 (24.32)	36 (39.56)	4.303	0.038*
Photophobia	40 (54.05)	50 (54.94)	0.013	0.909
Arthritis	60 (81.08)	81 (89.01)	2.065	0.151
Pleuritis	14 (18.91)	18 (19.78)	0.019	0.889
Pericarditis	10 (13.51)	10 (10.98)	0.244	0.621
Nephritis	45 (60.81)	39 (42.85)	5.264	0.021*
Neurological manifestation	12 (16.21)	13 (14.28)	0.118	0.731
Fever	46 (62.16)	45 (49.45)	2.666	0.102
Haematological abnormalities	45 (60.81)	64 (70.32)	1.649	0.199

[Table/Fig-1]: Clinical manifestation in childhood SLE patients and adult SLE patients.
*A p-value <0.05 is considered to be statistically significant

Parameters	Childhood onset SLE group (n=74), Number (%)	Adult SLE group (n=91) Number (%)	χ^2	p-value
Anaemia	40 (54.05)	60 (65.93)	2.4126	0.120
Leucopenia	32 (43.24)	41 (45.05)	0.0543	0.815
Thrombocytopenia	10 (13.51)	14 (15.38)	0.115	0.734

[Table/Fig-2]: Distribution of various haematological features in childhood onset and adult onset SLE patients.
Chi-square test between haematological features of childhood onset and adult onset SLE patients; Many patients had two or more of these features

Reduction in serum complement C3 and C4 were significantly more common in childhood onset SLE patients as compared to adult patients (p<0.05). Screening test for ANA was positive in all patients of both childhood onset SLE and adult SLE. Anti-dsDNA was the most commonly detected autoantibody in both paediatric (74.32%) and adult patient groups (51.64%). Anti-dsDNA was also significantly more frequent in childhood onset SLE cases as compared to adult cases (p=0.003). Anti-Sm, anti-SSA, anti-SSB, anti-RNP, anti-centromere, anti-Jo-1 and anti-Scl-70 antibodies were more frequently positive in adult SLE patients as compared to children but the difference was not statistically significant [Table/Fig-3].

Parameters	Childhood onset SLE patient (n=74) Number (%)	Adult SLE patient (n=91) Number (%)	χ^2	p-value
Anti-dsDNA	55 (74.32)	47 (51.64)	8.891	0.003*
Anti-Sm	21 (28.37)	30 (32.96)	0.402	0.525
Anti-RNP	25 (33.78)	34 (37.36)	0.227	0.633
Anti-SSA	23 (31.08)	36 (39.56)	1.277	0.258
Anti-SSB	15 (20.27)	19 (20.87)	0.009	0.923
Anti-centromere	2 (2.7)	5 (5.49)	0.783	0.376
Anti-Scl-70	2 (2.7)	3 (3.29)	0.049	0.825
Anti-Jo-1	1 (1.35)	2 (2.19)	0.164	0.685
Reduced complement C3	41 (55.40)	27 (29.67)	11.156	0.0008*
Reduced complement C4	35 (47.29)	11 (12.9)	25.163	<0.001*

[Table/Fig-3]: Serum complement and autoantibody profile in childhood onset SLE patients group and adult SLE patients group.
*A p-value <0.05 is considered to be statistically significant

DISCUSSION

In the present study, females were commonly affected by SLE in both childhood onset SLE and adult SLE group. However, the frequency of male patient involved in childhood onset SLE group (20.27%) was more than adult group (16.48%). Similar findings were present in previous studies on Indian population [5,6]. Studies from different parts of the world also had similar findings [12-16]. In contrast to present study findings, studies by Pande I et al., reported almost similar female:male ratio in both childhood onset SLE patients and adult SLE patients [6]. In the present study, the mean age of presentation in childhood onset SLE patients was 13.05 years and majority of patients (68.92%) belonged to 12-18 years age range. Similar results were noted in previous studies [7,17,18]. In present study, around 12.16% of patients presented with SLE within 5 years of age. Kini S et al., reported 6.25% of cases within 5 years of age [7]. Study from West Bengal detected 4 (9%) children, who had disease onset before the age of 5 years [8]. In contrast to present study findings, one study from North India by Pande I et al., and other study from South India by Chandrasekaran AN et al., did not report any case of SLE disease onset before 5 years of age [6,9]. Influence of age on genetic risk factors and inheritance is reported in many studies and childhood onset SLE is considered to have a higher genetic susceptibility than adult onset SLE [19].

In present study, arthritis was the most common (81.08%) clinical manifestation in both childhood onset SLE and adult patients of

SLE (89.01%), but there was no significant difference in incidence of arthritis between the two groups. Many other studies also found that arthritis was the common clinical presentation in both patient groups in their study [6,16]. However, few other studies observed arthritis was significantly more common in adult as compared to children [14] or vice versa [20]. Malar rash was significantly more common (p=0.001) in childhood onset SLE patients as compared to adult SLE patients. Similar findings were present in few previous studies [6,12,16,18]. One study from Oman reported, more significant occurrence of malar rash in adult SLE patients as compared to children [20]. Pradhan V et al., and El-Garf K et al., found no significant differences in incidence of malar rash in adult and paediatric SLE patients [5,14]. The frequency of renal involvement in paediatric lupus patients in Indian studies varies from 49.15 to 87.5% [5-10]. In the present study, renal involvement was detected in 60.81% of childhood onset SLE cases and significantly more common in childhood SLE cases as compared to adult cases (p=0.021). Similar findings were noted in earlier Indian studies and studies from different regions of the world [6,14,20-23]. In contrast to present study findings, Pradhan V et al., reported more significant renal involvement in adult SLE patients compared to children [5]. Study by Kim H et al., found low incidence of renal abnormalities in paediatric SLE patients (33.9%) and did not find any significant difference in renal involvement both paediatric and adult SLE group [12]. In the present study, oral ulcer was more commonly seen in adult SLE patients as compared to childhood onset SLE patients and this difference was significant (p=0.038). Similar finding was observed by Kim H et al., and El-Garf K et al., [12,14]. However few studies reported contradictory findings [16,22]. Indian study by Pradhan V et al., did not find any significant difference in incidence of oral ulcers between two groups, and neither did Al Rasbi A et al., in a study from Oman [5,20]. Many earlier studies found neurological manifestations were significantly more common in childhood onset SLE patients, but no significant difference between two groups were observed [5,12,14]. Choi JH et al., also noted findings similar to present study [22]. A study from South-east Asia also described most commonly affected systems to be haematological, renal, and mucocutaneous in childhood onset SLE [16]. Clinical manifestations of paediatric SLE patients in previous Indian studies along with the present study are shown in [Table/Fig-4] [5-10].

ANA positivity in childhood onset SLE varies from 96.9% to 100% in published studies [14-16,18,24]. In the present study, all the childhood onset SLE patients were positive for ANA. Previous Indian studies also had similar serological ANA positivity [5,6]. Among various autoantibodies, anti-dsDNA was most commonly detected in childhood onset SLE patients. Anti-dsDNA positivity in childhood onset SLE was significantly more common as compared to adult onset SLE patients. Studies by Joo YB et al., and Hoffman IE et al., reported findings similar to the present study [15,21]. However, Kim H et al., and El-Garf K et al., did not find significant difference in anti-dsDNA positivity between the two groups [12,14]. Present study and other studies comparing and contrasting prevalence of autoantibodies in childhood onset and adult onset SLE patients are tabulated in [Table/Fig-5] [12,14,15,21].

In present study, extractable nuclear antigen antibodies like anti-Sm, anti-RNP, anti-SSA, anti-SSB, anti-Jo-1, anti-centromeric and Scl-70 were more prevalent in adult SLE patients than childhood onset SLE patients but the difference between two groups was not statistically significant. In contrast to present study, Kim H et al., reported anti-Sm antibody positivity was significantly more common in childhood onset SLE, but El-Garf K et al., reported significantly increased occurrence of anti-Sm in adult SLE patients [12,14]. Joo YB et al., and Hoffman IE et al., did not detect significant differences in prevalence of anti-Sm antibodies in both groups [15,21]. Study by Kim H et al., observed that anti-RNP positivity was significantly more common in childhood onset SLE [12]. In contrast to present study findings, few earlier studies reported anti-SSA significantly more prevalent in adult SLE patient [15,18]. Similar to present study, Choi JH et al., found that prevalence of anti-Jo-1, anti-centromeric and Scl-70 were more common in adult SLE patients than childhood onset SLE patients but the difference between two groups was not significant [22]. However, Tarr T et al., found that anti-Jo-1 positivity was significantly more common in children as compared adult SLE patients [18]. In a very recently published study, on juvenile SLE patients, all were ANA positive, majority showed anti-dsDNA positivity (83%). Other antibodies including anti-RNP (41%), anti-Sm (31%), anti-SSA (27%), and anti-SSB (20%) positivity were seen in the same study, which was comparable to present study results [24]. In the present study, reduction in serum complement C3 and C4 level was noted more frequently in childhood onset SLE patients as compared to adult SLE patients and the difference was statistically significant. One earlier Indian study and studies from other parts of world also noted similar findings [6,14,20]. Abdel-Nabi HH and Abdel-Noor RA reported significant reduction in C4 levels in childhood onset SLE patients as compared to adult SLE patients but the reduction in C3 level was not significant [25]. Pradhan V et al., from India did not find any significant difference in complement levels between paediatric and adult SLE patients [5].

Clinical manifestations	Pande I et al., [6] age of patient included <16 y (n=83)	Chandrasekaran AN et al., [9] age of patient included <16 y (n=59)	Pradhan V et al., [5] age of patient included <14 y (n=25)	Mondal R et al., [8] age of patient included <12 y (n=44)	Agarwal I et al., [10] age of patient included <15 y (n=70)	Kini S et al., [7] age of patient included <18 y (n=32)	Present study age of patient included <18 y (n=74)
Place of study and year of publication	New Delhi, 1993	Madras, 1994	Mumbai, 2013	Kolkata, 2010	Tamil Nadu, 2009	Karnataka, 2020	Uttar Pradesh
Malar rash	83.1%	69.4%	44.0%	54.0%	57.1%	53.1%	64.86%
Alopecia	83.1%	49.0%	NA	20.0%	45.7%	12.5%	47.29%
Oral ulcers	NA	37.2%	12.0%	20.0%	NA	21.9%	24.32%
Photosensitivity	73.5%	20.3%	NA	NA	51.4%	6.3%	54.05%
Arthritis	90.4%	86.6%	60.0%	68.0%	65.7%	25.0%	81.08%
Pleuritis	28.9%	22.0%	NA	NA	2.8%	6.3%	18.91%
Pericarditis	28.9%	10.2%	NA	6.8%	2.8%	31.3%	13.51%
Nephritis	78.8%	49.1%	52.0%	54.0%	77.1%	87.5%	60.81%
Neuro-psychiatric manifestations	19.3%	27.1%	24.0%	25.0%	21.4%	31.3%	16.21%
Fever	89.2%	79.8%	16.0%	68.1%	94.2%	71.9%	62.16%

[Table/Fig-4]: Clinical manifestations of paediatric SLE patient in previous Indian studies.
*NA=Data not available

Type of antibodies	Study groups	Kim H et al., [12]	Joo YB et al., [15]	El-Garf K et al., [14]	Hoffman IE et al., [21]	Present study
Anti-dsDNA	Children	66.2%	91.0%	66.3%	60.7%	74.32%
	Adult	59.0%	82.8%	58.8%	24.9%	51.64%
	p-value	0.059	0.024	0.083	<0.001	0.003
Anti-Sm	Children	29.6%	18.9%	0.7%	17.9%	28.37%
	Adult	22.0%	14.0%	5.0%	12.4%	32.96%
	p-value	0.024	0.172	0.017	NS	0.525
Anti-RNP	Children	33.6%	26.7%	0.7%	14.3%	33.78%
	Adult	16.6%	32.0%	1.8%	17.5%	37.36%
	p-value	<0.001	0.260	0.445	NS	0.633
Anti-SSA	Children	33.6%	26.7%	7.8%	23.2%	31.08%
	Adult	26.7%	40.2%	6.8%	33.5%	39.56%
	p-value	0.076	0.004	0.681	NS	0.258
Anti-SSB	Children	17.1%	6.9%	7.8%	7.1%	20.27%
	Adult	11.7%	7.4%	1.5%	17.0%	20.87%
	p-value	0.068	0.975	<0.001	NS	0.923

[Table/Fig-5]: Antinuclear Antibodies (ANA) and serum complement levels in childhood onset SLE patient group and adult SLE patient group.
**NS=statistically not significant

Limitation(s)

Since, present study was conducted in limited number of patients from a single centre, further studies involving large sample size is required to confirm present study findings. The present study was a retrospective study, and involving very young children, some clinical features could have been missed.

CONCLUSION(S)

The age of onset of SLE influences clinical manifestation and autoantibody positivity. Authors found many similarities and also few important differences in demographic features, clinical presentations and antibody profile of childhood onset SLE and adult SLE patients. Renal involvement and malar rash were more common in children however, oral ulcer was more common in adult SLE patients. Among serological parameters, anti-dsDNA positivity and reduction in complement C3 and C4 levels were significantly more common in childhood onset SLE. Detection of nephritis at an early stage should be the prime concern in childhood SLE which may help in reducing mortality. Reduced complement levels indicate increased activity in childhood SLE as compared to adults suggesting aggressive course of childhood SLE.

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