Original Article

Clinical Differences in Lupus Nephritis in Thai Patients with Systemic Lupus Erythematosus with Positive vs. Negative Anti-dsDNA Antibody

Sirikan Nittayawan, MD[1], Chingching Foocharoen, MD[1], Ajanee Mahakkanukrauh, MD[1], Ratanavadee Nanagara, MD[1], Siraphop Suwannaroj, MD[1]

[1] Department of Medicine, Khon Kaen University, Khon Kaen, Thailand

Objective: Anti-double strand deoxyribonucleic antibody (anti-dsDNA) is thought to trigger tissue inflammation-particularly in the kidney-in systemic lupus erythematosus (SLE). The association between anti-dsDNA and lupus nephritis (LN) has not been reported among Thais. The authors aimed to define the association between the clinical characteristics of positive vs. negative anti-dsDNA antibody in patients having SLE with LN.

Materials and Methods: A historical cohort was conducted of SLE patients followed-up at Srinagarind Hospital, Khon Kaen University, Thailand, between January 2009 to December 2013. The authors excluded patients not tested for anti-dsDNA.

Results: Of 132 SLE patients, the female was 123 cases. The respective mean age at onset and mean age during the study was 28.0±11 and 35.2±11.2 years. The mean duration of disease was 5.7±4.7 years. Ninety-six cases were tested for anti-dsDNA, of whom 73 (76%) were positive. There was a significant association between the presence of anti-dsDNA antibody and subnephrotic range proteinuria (p=0.048) and negative association with LN class IV A/C at onset (p=0.04).

Conclusion: Anti-dsDNA was positive in around three-quarters of Thai SLE patients and the presence of the antibody was associated with renal involvement, particularly subnephrotic range proteinuria.

Keywords: Systemic lupus erythematosus; Autoimmune diseases; Anti-dsDNA antibody; Lupus nephritis; Proteinuria

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Systemic lupus erythematosus (SLE) is a serious autoimmune disease occurring most commonly in women[1-3]. The disease may cause organ inflammation and permanent structural damage. Lupus nephritis (LN) is one of the serious internal organ inflammations caused by SLE. Clinical presentations of LN include edema of the legs, hypertension, proteinuria, and/or renal failure. LN is classified into six types according to the renal pathology according to the International Society of Nephrology (ISN) and the 2003 Renal Pathology Society (RPS): Class I – Minimal mesangial lupus nephritis; Class II – Mesangial proliferative lupus nephritis; Class III – Focal lupus nephritis (active and chronic; proliferative and sclerosing); Class IV – Diffuse lupus nephritis (active and chronic; proliferative and sclerosing; segmental and global); Class V – Membranous lupus nephritis; and, Class VI – Advanced sclerosis lupus nephritis or the end-stage of LN[1]. Proteinuria is the most common abnormal urine finding in all classes of LN. Heavy proteinuria is a classical presentation in Class V whereas urine sediment is more common in classes III and IV.

Anti-double strand deoxyribonucleic antibody (anti-dsDNA) is a specific autoantibody in SLE with a prevalence of 40 to 60%[4,5]. Anti-dsDNA antibody is an autoantibody thought to trigger tissue inflammation in SLE, particularly of the kidney. The study revealed that the detection of anti-dsDNA antibody in SLE patients was associated with the severity of LN[2,3,6,7]. The mechanism is supported by the discovery of a high affinity of anti-dsDNA antibody to bind with the mesangial tissue in the kidney. The binding of annexin II—expressed on the glomerular—and anti-dsDNA antibody correlates with disease activity in LN[8]. The negative association between anti-dsDNA and the severity of LN has been reported[9,10]. There have been, moreover, case reports of immune complex deposits in the kidneys of LN patients[11]. Anti-dsDNA antibody might then be predictive of the outcome of LN in SLE patients. Due to the respective positive and negative association between anti-dsDNA antibody and the severity of LN, and the low numbers of patients in most studies, we aimed to clarify the association between the clinical characteristics of positive vs. negative anti-dsDNA antibody in LN patients.

Correspondence to:

Suwannaroj S.

Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

Phone: +66-43-363746, +66-43-363664

Email: siraphop@kku.ac.th

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Materials and Methods

A historical cohort study was conducted in adult SLE patients followed-up at the Out-patient Clinic or admitted to Srinagarind Hospital, Khon Kaen University, Thailand, between January 2009 and December 2014. All medical records giving a diagnosis of SLE were reviewed according to the revised 1997 American College of Rheumatology (ACR) criteria[12]. We excluded patients diagnosed SLE overlap or other connective tissue diseases.

Laboratory method

The authors performed immunofluorescence assay (IFA) anti dsDNA test using the BioSystems anti-dsDNA antibody test designed for this purpose. The main substrate is flagellate *Crithidia lucillae,* which contains kinetoplast with numerous molecules of double stranded circular DNA. Serum specimens were maintained at room temperature for at least half an hour. Buffer was diluted with distilled water to a final 1x concentration. Serum specimens were diluted with buffer. One drop of diluted serum—for both the specimens and controls—were added into slide wells. After the incubation and rinsing procedures, IgG FITC-EVANS was added and lastly several drops of mounting medium. The slides were examined by fluorescence microscope (495 nm excitation filter and 525 nm emission filter). Positive serum specimens were titrated to the end-point dilution defined as the highest dilution giving a positive result. A finding was positive only in the event of kinetoplast fluorescent illumination. Nuclei, basal body, or flagellum illumination did not constitute a positive finding for anti-dsDNA. IFA anti-dsDNA is reported qualitatively (positive or negative)[13,14].

Operational definitions

An anti-dsDNA titer >1:40 was considered positive. The subnephrotic range proteinuria was 150 mg to 3.5 g per 24 h[15] Leukopenia was defined when white blood cell count from complete blood count (CBC) test was <4,000 cells/mm^3 and lymphopenia was defined when the absolute lymphocyte count was <1,000 cells/mm^3[16]. LN was definited by kidney biopsy and the histopathology was classified according to The Revised International Society of Nephrology/Renal Pathology Society classification for lupus nephritis[17]. LN remission was defined when proteinuria <0.3 g per 24 h (UPCR <300 mg/g [<30 mg/mmol]) or partial remission was defined as proteinuria >0.3 but <3.5 g per 24 h or a decrease in proteinuria by at least 50% from the initial value and <3.5 g per 24 h[18].

Statistical analysis

The data were categorized into dichotomous, polytomous, or continuous variables. The clinical characteristics were reviewed to determine differences between anti-dsDNA positive and negative in Thai patients with SLE. The categorical data were tested for significance using the X^2 or Fisher's exact test. The continuous data were analysed using the Student t-test or Wilcoxon ranksum, according to whether the data had a normal or abnormal distribution, respectively. The odds ratio (OR) with a respective 95% CI and p-value were used to determine the clinical difference between anti-dsDNA antibody positive and negative. All statistical tests were two-tailed and a p-value of <0.05 was considered statistically significant. All data analyses were performed using STATA version 16.0 (StataCorp., College Station, TX, USA).

The study was approved by the Human Research Ethics Committee of Khon Kaen University per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE581156). The company supplying the antibody had no role in the study.

Results

Among the 132 SLE patients, the female to male ratio was 123:9. The respective mean age at onset and mean age during the study was 28.0±11 and 35.2±11.2 years. The duration of disease was 5.7±4.7 years. Ninety-six cases were tested for anti-dsDNA, of whom 73 (76%) were positive. Cases were commonly females than males whether the anti-dsDNA was positive or negative. The mean age at onset in both the anti-dsDNA positive and negative was comparable (29.2 vs. 28.5 years). The anti-dsDNA positive patients seemed to have more constitutional symptoms than those who were anti-dsDNA negative albeit there was no statistically significant difference. Others clinical characteristics were not significantly different (Table 1). The baseline demographics and overall clinical characteristics of the SLE patients between SLE (anti-dsDNA positive and negative) are presented in Table 1.

The presentation of LN at onset and during follow-up were not significantly different between the patients who were anti-dsDNA positive vs. negative. Notwithstanding, the patients who were anti-dsDNA positive had significantly less spot urine protein/creatinine ratios at onset and at 1st LN flare than those who were anti-dsDNA negative (p=0.048 and 0.001, respectively). When performing subgroup analysis by LN class, LN class IV A/C was less frequently found at onset among those who were anti-dsDNA positive (p=0.04). The numbers of LN flare during follow-up among patients who were anti-dsDNA positive trended to be greater than those who were negative, albeit the difference was not statistically significant (Table 2). The renal manifestations between patients anti-dsDNA positive vs. negative are presented in Table 2.

Overall renal outcomes were fair. The majority of patients had LN partial remission; 8 of 18 (44.4%) had partial remission after the 1st LN flare; 5 of 10 (50%) after the 2nd LN flare; and, 3 of 4 (75%) after the 3rd LN flare, but only 2 patients died after the 1st LN flare. One patient died due to a *Escherichia coli*-catheter-related blood stream infection and one due to septicemia. The renal outcomes of the anti-dsDNA positive and negative patients are presented in Figure 1 to 4. In 2nd flare, two SLE patients were anti-dsDNA negative, and both were LN class IV A/C, whose disease was in remission. In the 3rd flare, all of the patients were anti-dsDNA positive (Figure 4).

Table 1. Baseline demographics and clinical characteristics between patients who were anti-dsDNA positive vs. negative

Characteristic	Anti-dsDNA positive (n=73)	Anti-dsDNA negative (n=23)	p-value
Age (years); mean±SD	29.2±12.4	28.5±8.3	0.82
Female sex (%)	66 (67.7)	23 (100)	0.19
Clinical characteristic (%)			
Fever	16 (21.9)	2 (8.7)	0.22
Weight loss	5 (6.8)	1 (4.3)	0.99
Fatigue	9 (12.3)	1 (4.3)	0.44
Arthritis	31 (42.4)	5 (21.7)	0.09
Oral ulcer	20 (27.4)	8 (34.8)	0.60
Discoid rash	23 (31.5)	9 (39.1)	0.61
Malar rash	22 (30.1)	5 (21.7)	0.59
Photosensitivity rash	11 (15.0)	4 (17.4)	0.75
Vasculitis	13 (17.8)	3 (13.0)	0.75
Pleuritis	4 (5.4)	2 (8.7)	0.63
Pericarditis	2 (2.7)	1 (4.4)	0.57
Hemolytic anemia	30 (41.1)	9 (39.1)	1.00
Leukopenia	19 (26.0)	3 (13.0)	0.26
Lymphopenia	14 (19.2)	2 (8.7)	0.34
Thrombocytopenia	6 (8.2)	4 (17.4)	0.25
Seizure	4 (5.5)	1 (4.4)	1.00
Psychosis	2 (2.7)	1 (4.4)	0.57
Cognitive impairment	1 (1.3)	0	1.00

SD = standard deviation

Discussion

Anti-dsDNA presents in ~76% of Thai SLE. The prevalence is higher than previous studies[4,5], perhaps because of the technique used in the serologic test. An ELISA test was used for anti-dsDNA detection in previous studies[19] while the IFA technique was used in our study. Anti-dsDNA detection by ELISA has more specificity but less sensitivity than the IFA technique. Owing to the different sensitivity and specificity of the tests, the prevalence of anti-dsDNA among Thai SLE was higher than in other studies. Another reason for the higher prevalence of anti-dsDNA among Thai SLE might be a selection bias; as all of the patients had undergone antibody testing at onset. The patients who did not fulfill the SLE criteria might have been tested for anti-dsDNA in order to make a definite diagnosis (using the ACR criteria), while those who were clinically definite for SLE were not tested.

Our study revealed that the presence of anti-dsDNA had lower range of proteinuria and less frequent of LN class IV A/C than those who were antibody negative. The finding can be explained by the pathogenic mechanism of anti-dsDNA. Previous in vivo studies reported that intra-glomerular electron-dense deposits containing extracellular chromatin fragments are targets of the nephritogenic antibody; it is a two-step process that involves the pathogenesis of LN: (a) it begins with mild mesangial proliferation (b) culminating in membranoproliferative nephritis with immune complex deposition[20-22]. Disease progression in this model is attributed to a loss of renal DNase I activity that increases the matrix metalloproteinase-2 (MMP-2) activity and leads to larger chromatin fragments retained in the glomerular basement membrane (GBM). Subsequently, the immune cells are activated to GBM[23-26]. The potential mechanisms for lupus nephritis of anti-dsDNA appear to be related to the LN class. Our results indicate that anti-dsDNA particularly at onset not only helps in making the diagnosis of SLE but can also be a clue to the renal manifestation and renal pathology among SLE patients. Our findings provide an informational guide for predicting the LN class and planning initial treatment of LN in cases where kidney biopsy is not available, is denied, or having such creates a risk of complications.

Table 2. Renal manifestations between anti-dsDNA positive vs. negative patients

Feature	Anti-dsDNA positive (n=73)	Anti-dsDNA negative (n=23)	p-value
LN at onset	23 (31.5)	9 (39.1)	0.61
LN class II	2 (2.7)	1 (4.4)	0.57
LN class III	6 (8.2)	0	0.33
LN class IV A/C	8 (11.0)	7 (30.4)	0.04*
LN class IV A/G	5 (6.9)	0	0.33
LN class IV C/G	1 (1.4)	0	0.99
LN class IV AC/G	1 (1.4)	0	0.99
LN class V	1 (1.4)	1 (4.4)	0.42
UPCI; median (IQR)	1.24 (0.72 to 2.89)	2.59 (1.75 to 6.27)	0.048*
Duration of disease at 1st LN flare (years); mean±SD	2.35±3.12	1.75±2.0	0.76
Classification of LN at 1st flare	15 (20.6)	3 (13.0)	0.55
LN class II	1 (1.4)	1 (4.4)	0.42
LN class III	4 (5.5)	0	0.33
LN class IV A/C	8 (11.0)	0	0.19
LN class IV A/G	1 (1.4)	1 (4.4)	0.42
LN class IV C/G	0	0	-
LN class IV AC/G	1 (1.4)	1 (4.4)	0.42
LN class V	0	0	-
UPCI; mean±SD	2.46±1.88	8.18±5.82	0.001*
Duration of disease at 2nd LN flare (years); mean±SD	6.54±6.09	5.72±0.44	0.88
Classification of LN at 2nd flare	8 (11.0)	2 (8.7)	0.76
LN class II	0	0	-
LN class III	0	0	-
LN class IV A/C	5 (6.9)	2 (8.7)	0.67
LN class IV A/G	0	0	-
LN class IV AC/G	1 (1.4)	0	1.00
LN class V	2 (2.7)	0	1.00
UPCI; mean±SD	3.66±3.34	3.15±2.21	0.75
Duration of disease at 3rd LN flare (years); mean±SD	9.3±8.3	-	-
Classification of LN at 3rd flare	4 (5.5)	0	0.57
LN class II	0	0	-
LN class III	0	0	-
LN class IV A/C	3 (4.1)	0	0.99
LN class IV A/G	0	0	-
LN class IV AC/G	1 (1.4)	0	0.99
LN class V	0	0	-
UPCI; mean±SD	4.71±3.44	0	-

* Statistically significant
UPCI = Spot urine protein/creatinine ratio

The renal outcome of Thai SLE, anti-dsDNA negative patients trended better than anti-dsDNA positive patients. Due to the low number of LN in anti-dsDNA negative patients, there was insufficient statistical power to diffentiate the different outcomes. The majority of anti-dsDNA positive patients had fair renal outcomes: nearly half

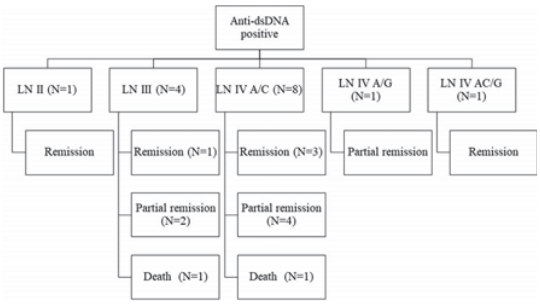

Figure 1. Outcome of the 1st LN flare in SLE among anti-dsDNA positive patients.

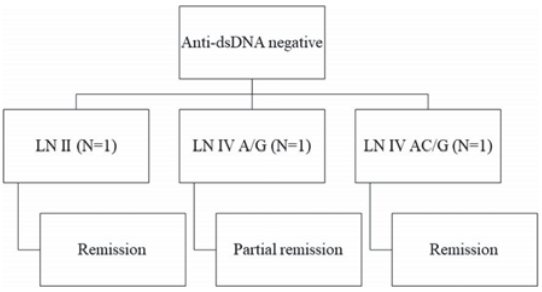

Figure 2. Outcome of 1st LN flare in SLE among anti-dsDNA negative patients.

had no renal remission after the 1st LN flare and the rate of remission trended to be lower during follow-up compared to the previous flare. The previous outcome of LN—which was not in remission—might influence the next renal outcome. A previous study reported that anti-dsDNA levels often correlate with disease activity[27] and longitudinal follow-up on anti-dsDNA levels might be useful for predicting the risk of renal flare[28]. Matthew, et al described how the reduction in the anti-dsDNA level is associated with a reduced risk of renal flare[28]. We did not, however, conduct a longitudinal follow-up on anti-dsDNA levels or titers, so we cannot comment on the different renal outcomes between persistent anti-dsDNA positive and persistent anti-dsDNA negative.

Our study had some limitations, including: A) The low number of patients included in the study, which might influence the power of statistical analysis; B) We did not use the Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC) for diagnosing SLE because the patients were included before the classification criteria was launched; C) We have no data on the association between changing anti-dsDNA levels and renal manifestations/outcomes because only a few cases repeated the anti-dsDNA test; D) The titer or the level of anti-dsDNA was not available

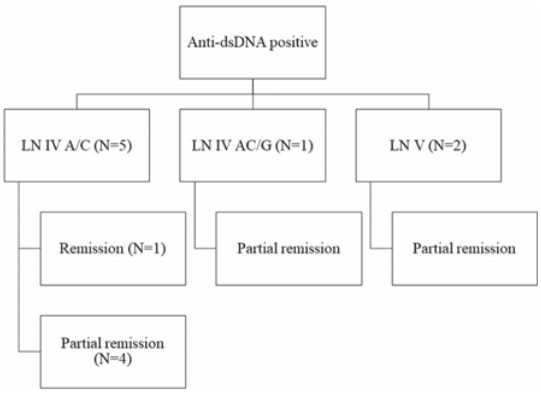

Figure 3. Outcome of 2nd LN flare in SLE among anti-dsDNA positive patients.

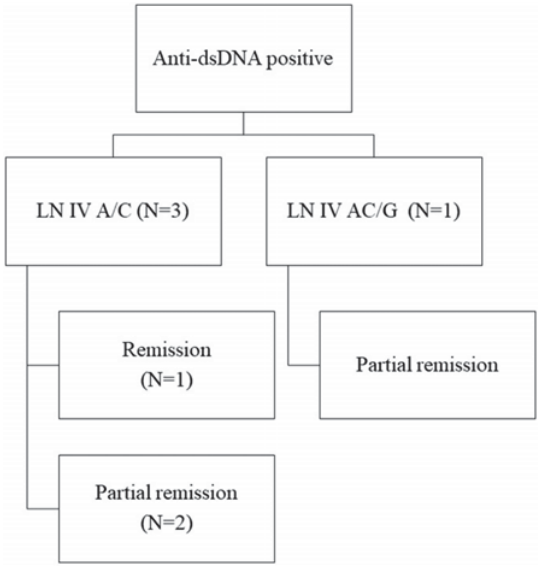

Figure 4. Outcome of 3rd LN flare in SLE among anti-dsDNA positive patients.

because of a limitation of the serological test, so we cannot determine the difference in renal manifestations according to the anti-dsDNA titer; and, E) Kidney biopsy was not performed on all of the patients who had mild lupus nephritis. Notwithstanding these limitations, our data do provide some value for attending physicians who are monitoring renal manifestations and renal outcomes among Thai SLE patients—whether or not they are anti-dsDNA positive.

Conclusion

Around three-quarters of the Thai SLE patients

were anti-dsDNA positive and the presence of the antibody was associated with renal involvement; particularly in those with subnephrotic range proteinuria.

What is already known on this topic?

Anti-dsDNA is a specific autoantibody in SLE which is thought to trigger tissue inflammation in SLE, particularly of the kidney. Anti-dsDNA antibody might then be predictive of the outcome of LN in SLE patients.

What this study adds?

Positive for anti-dsDNA was associated with renal involvement; particularly in LN class IV and those with subnephrotic range proteinuria. Anti-dsDNA might a guide for predicting the LN class and planning initial treatment of LN in cases where kidney biopsy is not available, is denied, or having such creates a risk of complications.

Declarations

Ethics approval

The Human Research Ethics Committee of Khon Kaen University reviewed and approved the study per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE581156).

Consent for publication

All of the authors consent to publication and grant the publisher exclusive license of the full copyright.

Availability of data and material

Data available on reasonable request.

Funding statement

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Author contributions

SN collected the data and drafted the manuscript. CF and SS conceived and designed the study. CF, SS, AM, SN, and RN read and commented on the manuscript.

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Potential conflicts of interest

The authors declare no conflict of interest.

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