Medicina Clínica Práctica 5 (2022) 100321

MEDICINA CLINICA PRÁCTICA

www.elsevier.es/medicinaclinicapractica

Original article

The correlation between the levels of anti-dsDNA IgA antibody and the severity of systemic lupus erythematosus based on cutaneous vasculitis

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ARTICLE INFO

Article history:
Received 10 December 2021
Accepted 10 January 2022
Available online 2 March 2022

Keywords:
Systemic lupus erythematosus
cutaneous vasculitis
IgA anti-dsDNA

ABSTRACT

Background: The purpose of this study was to examine the association between anti double-stranded DNA (anti-dsDNA) IgA levels and the severity of systemic lupus erythematosus (SLE) regarding the presence of cutaneous vasculitis.
Method: The cross-sectional study was conducted at the outpatient installation of Wahidin Sudirohusodo Hospital and Hasanuddin University hospital in Makassar from September 2020 to February 2021. Investigation of anti-dsDNA IgA levels in SLE patients was performed in two groups: group A (SLE patients with cutaneous vasculitis) and group B (SLE patients without cutaneous vasculitis). The diagnosis of cutaneous vasculitis was based on the presence of efflorescence in the form of erythematous macules and papules, petechiae, urticaria, purpura, nodular lesions and ulcerated lesions. To assess the severity of SLE, the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI) was employed; the SLE is severe if the value ranges from 11 to 19 and very severe if the value >20. Chi square and Fisher Exact were used in statistical analysis. The results are significant if the p value <0.05.
Result: 54 subjects with SLE patients were identified. The mean age of the subjects in group A was 29.6 ± 7.6 years and in group B 29.9 ± 9.5 years where there were more women in both groups. The most skin manifestations of the entire sample were petechiae with 27.6%. In subjects with positive anti-dsDNA IgA, group A was found to be 100% and significantly higher than in group B at 72.0%. Meanwhile, in subjects with moderate, severe and very severe SLE, the percentages of group A were 37.9%, 48.3% and 13.8%, respectively, which were significantly higher than group B with 20.0%, 44.0%. and 0.0%. Furthermore, in moderate, severe and very severe SLE, the percentage of positive anti-dsDNA IgA (31.9%, 51.1% and 8.5%) was significantly higher than the negative (14.3%, 14.3% and 0.0%). Meanwhile, the mild degree was found to be higher in the negative anti-dsDNA IgA (71.4%) than the positive (8.5%) with p value = 0.002.
Conclusion: Anti-dsDNA IgA levels are related to the severity of disease in SLE patients based on cutaneous vasculitis. Therefore, anti-dsDNA IgA levels and the presence of cutaneous vasculitis may be useful as the potential predictors of disease severity in SLE patients.

La correlación entre los niveles de anticuerpo iga anti-dsdna y la gravedad del lupus eritematoso sistémico basado en la vasculitis cutánea

Palabras clave:
lupus eritematoso sistémico
vasculitis cutánea
IgA anti-dsDNA

RESUMEN

Antecedentes: El propósito de este estudio fue examinar la asociación entre los niveles de IgA anti-dsDNA y la gravedad del LES con respecto a la presencia de vasculitis cutánea.
Método: el estudio transversal se realizó en las instalaciones para pacientes ambulatorios del Hospital Wahidin Sudirohusodo y el Hospital Universitario Hasanuddin en Makassar desde septiembre de 2020 hasta febrero de

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https://doi.org/10.1016/j.mcpsp.2022.100321

2021. La investigación de los niveles de IgA anti-ds-DNA en pacientes con LES se realizó en dos grupos: grupo A (pacientes con LES con vasculitis cutánea) y grupo B (pacientes con LES sin vasculitis cutánea). El diagnóstico de vasculitis cutánea se basó en la presencia de eflorescencias en forma de máculas y pápulas eritematosas, petequias, urticaria, púrpura, lesiones nodulares y lesiones ulceradas. Para evaluar la gravedad del LES se empleó el Índice de Actividad de la Enfermedad del Lupus Eritematoso Sistémico Mexicano (MEX-SLEDAI); el LES es grave si el valor oscila entre 11 y 19 y muy grave si el valor es >20. En el análisis estadístico se utilizaron Chi cuadrado y Fisher Exact. Los resultados son significativos si el valor de p <0,05.

Resultado: se identificaron 54 sujetos con pacientes con LES. La edad media de los sujetos del grupo A fue de 29,6 ± 7,6 años y del grupo B de 29,9 ± 9,5 años donde había más mujeres en ambos grupos. La mayor manifestación cutánea de toda la muestra fueron las petequias con un 27,6%. En sujetos con anti-dsDNA IgA positivo, se encontró que el grupo A era del 100 % y significativamente más alto que en el grupo B con un 72,0 %. Por su parte, en sujetos con LES moderado, severo y muy severo, los porcentajes del grupo A fueron 37,9%, 48,3% y 13,8%, respectivamente, los cuales fueron significativamente superiores al grupo B con 20,0%, 44,0%. y 0,0%. Además, en LES moderado, grave y muy grave, el porcentaje de IgA anti-dsDNA positivo (31,9%, 51,1% y 8,5%) fue significativamente mayor que el negativo (14,3%, 14,3%). y 0,0%). Mientras tanto, se encontró que el grado leve era mayor en el anti-dsDNA IgA negativo (71,4 %) que en el positivo (8,5 %) con un valor de p = 0,002.

Conclusión: Los niveles de IgA anti-dsDNA están relacionados con la gravedad de la enfermedad en pacientes con LES con base en vasculitis cutánea. Por lo tanto, los niveles de IgA anti-dsDNA y la presencia de vasculitis cutánea pueden ser útiles como predictores potenciales de la gravedad de la enfermedad en pacientes con LES.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease involving various body systems with varied clinical manifestations and an unpredictable course of remission–relapse.[1,2] The production of pathogenic autoantibodies against nucleic acids and body-binding proteins as a result of intolerance to own body components is one of the hallmarks of SLE.[3]

North America has the highest estimated incidence and prevalence of SLE, with 23.2/100,000 people and 241/100,000 people per year, respectively.[4] In Indonesia, data on the prevalence of SLE is currently lacking. In three consecutive years, the number of rheumatology polyclinic visits in many Indonesian hospitals has increased, with 17.9–27.2% in 2015, 18.7–31.5% in 2016 and 30.3–27.5% in 2016. In 2017, the rate was 58%. Women are more likely than men to develop SLE.[5]

In SLE patients, the prevalence of vasculitis varies between 11 and 36%. Vasculitis is one of the primary causes of mortality in SLE patients, as it is characterized by inflammatory cell infiltration and necrosis of vessel walls.[6,7] The size of the vessels involved (arteries, veins, and/or capillaries) and the size of the vessels involved affect the clinical manifestations of this vascular inflammatory disease. Depending on the region of involvement (skin or internal organs), the prognosis might range from mild to severe. According to a review published in 2014 by Fabris et al, cutaneous vasculitis affects 19–28% of SLE patients in Europe. Furthermore, Ramos-Casal et al (2006) revealed that small vessel vasculitis was the most common kind of vasculitis among SLE patients with vasculitis in a cohort study conducted in Barcelona between 1980 and 2004. (SVV).[8]

Anti-dsDNA (anti double-stranded DNA) antibodies develop as a result of defective apoptotic material removal, resulting in an autoimmune reaction to self-antigens, particularly nucleosomes.[9] Anti-dsDNA antibodies are classified according to their isotype, avidity and idiotytype. Anti-dsDNA antibodies are known as immunoglobulin G (IgG), immunoglobulin M (IgM) and immunoglobulin A (IgA) based on the isotype.[10,11] IgG anti-dsDNA is a relatively specific marker for disease activity and plays an essential role in the emergence of clinical symptoms of SLE, particularly lupus nephritis. Anti-dsDNA IgM is protective against lupus nephritis and does not correlate with disease activity. Few studies have looked at the role of anti-dsDNA IgA in diagnosing and monitoring SLE, and the findings are equivocal.[9,10,11]

IgA is the most prolific antibody in the human body, outnumbering all other classes combined. IgA's immunological role is to bind and neutralize pathogens in the body's mucosa to avoid infection, but it also plays a role in the onset of inflammation, both mucosal and non-mucosal.[12]

The major mediator in skin problems is immunoglobulin A (IgA). In 2019, Smith et al found a higher level of IgA in the serum of SLE patients with discoid lesions compared to those who did not have cutaneous symptoms.[13] Kallas et al (2020) revealed that SLE patients with discoid lesions exhibited risk factors for developing cutaneous vasculitis in a cohort trial enrolling 2580 SLE patients.[14]

Witte et al. identified a connection between IgA anti-dsDNA and SLE activity and vasculitis in 1998.[15] Anti-dsDNA IgA was also associated with disease activity parameters such as increased erythrocyte sedimentation rate, complement component C3 and clinical parameters of vasculitis, such as acral necrosis and erythema, but not with clinical parameters of vasculitis with nephritis and arthritis, according to a study conducted by Andrejevic et al (2013).[9] Jia et al. (2018) found that IgA anti-dsDNA was a risk factor for disease activity, and that it was associated to joint abnormalities or vasculitis, and even perhaps to serositis ($p = 0.008$) and anemia ($p = 0.004$).[11] There is currently insufficient information on the correlation between anti-dsDNA IgA levels and the severity of SLE in Makassar based on cutaneous vasculitis.

Methods

From September 2020 to February 2021, a cross-sectional study was conducted at the outpatient facilities of Wahidin Sudirohusodo Hospital Makassar and Universitas Hasanuddin Hospital. Anti-ds-DNA IgA levels were measured in SLE patients who were separated into two groups: those with cutaneous vasculitis (group A) and those without cutaneous vasculitis (group B). With a titer of ≥0.50, anti-dsDNA IgA levels were positive. The study population was all subjects of SLE group A and group B who met the inclusion criteria. Inclusion criteria included: SLE group A and group B, female, aged 18–55 years, and met the criteria for SLE diagnosis based on ACR 1997, and subjects who were willing to participate in the study and signed an informed consent.

The presence of efflorescence in the form of erythematous macules and papules, petechiae, urticaria, purpura, nodular lesions and ulcerated lesions in the individual was used to diagnose cutaneous vasculitis. IgA ds-DNA levels are positive if the value is: 0.50 with the cut-off value (negative control <0.05) is 0.15 and the cut-off value (negative control ≥0.05): negative control + 0.10.

The Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI) was used to determine the severity of SLE, with a value

of 11–19 indicating severe SLE and a value of 20 indicating very severe SLE.

Consecutive sampling is used to obtain samples. Chi square and Fisher Exact statistical tests were employed to analyse the data in SPSS version 22. If the p value <0.05, the findings of statistical tests are considered significant.

Results

Analysis was performed on 54 SLE patients with and without cutaneous vasculitis. Table 1 shows that there are 29 samples (53.7%) with cutaneous vasculitis and 25 samples (46.3%) of SLE patients without cutaneous vasculitis. In addition, the average age of SLE patients with cutaneous vasculitis was 29.6 ± 7.6, while the average age of SLE patients without cutaneous vasculitis was 29.9 ± 9.5. Table 2 reveals that the two sample groups had more female subjects than males. The difference between the two groups was not statistically significant (p>0.05). Meanwhile, petechiae were the most prevalent symptoms reported in SLE patients with cutaneous vasculitis by 8 samples (27.6%).

In Table 3, the distribution of skin manifestation is dominated by petechiae (27,6%), followed by papules and necrosis with 24,1%.

Cutaneous vasculitis was identified in 100% of participants with positive anti-dsDNA IgA, which was significantly greater than the 72.0 percent found in subjects without cutaneous vasculitis. Table 4 shows a statistically significant association between positive anti-dsDNA IgA and the occurrence of cutaneous vasculitis in SLE (p <0.01).

In subjects with moderate, severe and very severe SLE, the percentages of cutaneous vasculitis were 37.9%, 48.3% and 13.8%, respectively, and were significantly higher than those without vasculitis with 20.0%, 44.0% and 0.0% (Table 5). In contrast to the patients with cutaneous vasculitis, the mild degree was reported to be higher in patients without vasculitis (36.0%) and (0.0%). The severity of the disease and the incidence of cutaneous vasculitis in SLE were found to have a statistically significant relationship (p<0.01).

The percentage of positive anti-dsDNA IgA in individuals with moderate, severe, and very severe SLE was 31.9%, 51.1% and 8.5%, respectively, and was substantially greater than the percentage of negative patients with 14.3%, 14.3% and 0.0%. Meanwhile, negative anti-dsDNA IgA was higher (71.4%) than positive anti-dsDNA IgA in mild degrees (8.5%). These findings revealed a statistically significant association between disease severity and positive anti-dsDNA IgA (p <0.01) (table 6).

Discussion

This study included 54 study subjects with two categories of SLE samples with cutaneous vasculitis and without cutaneous vasculitis, based on the age of subjects in SLE with cutaneous vasculitis was 29.6 ± 7.6 and in the group without vasculitis was 29.9 ± 9.5. This is in line with the European League Against Rheumatism (EULAR) data, whereas 65% of patients with SLE have disease onset between 18 and 55 years. Female subjects were found to be more frequent than males in both sample groups, and this is also consistent with EULAR data show that women are nine times more likely to develop SLE than men. This is related to hormonal factors where estrogen facilitates humoral responses, leading to increased B cell proliferation and antibody production.[16]

In this study, data were obtained from SLE patients with cutaneous vasculitis with manifestations ranging from the most common to the rare, namely, petechiae (8 subjects), papules, and necrosis (7 subjects), petechiae–papules–purpura (4 subjects), and necrosis (3 subjects). Cutaneous vasculitis was found in 19%–28% with a descriptive analysis of 704 SLE patients in Europe.[17] Vasculitis lesions of the SLE include palpable purpura, petechiae, papulonodular lesions, livingo reticularis, skin infarction, erythematous plaque, erythema with necrosis, panniculitis, hemorrhagic splintering and superficial ulceration.[16] Urticarial vasculitis is a variant of cutaneous small-vessel vasculitis (SVV). It is characterized by red and red patches or sores on the skin. The first symptom of urticarial vasculitis is an urticarial eruption (characterized by symptoms) that is often painful or burning.

In some cases, the complaint is itchy. Lesions are red patches or plaques that may have a white center, and petechiae may appear. Unlike urticaria, urticarial vasculitis lesions usually last for more than 24 hours in a fixed location, after which they slowly resolve spontaneously. Ecchymosis or hyperpigmentation may occur in the healing process.[18] This supports the results of the study of SLE subjects with clinical cutaneous vasculitis mostly found to have petechiae.

According to Witte et al., levels of anti-dsDNA IgA can be used to correlate disease activity and may be associated with the presence of cutaneous vasculitis.[15] Ramos-Casals et al. conducted a cohort study in Barcelona between 1980 and 2004, in which 76 of 540 patients (11%) found the presence of cutaneous vasculitis. There were skin lesions of primary clinical presentation in 68 (89%) patients, while the remaining 8 (11%) had visceral vasculitis; 65 (86%) patients had small vessel vasculitis (SVV), and 11 (14%) had moderate vascular vasculitis (MVV).[8]

One of the clinical manifestations of organ involvement from SLE is the presence of cutaneous vasculitis and, according to the Indonesian Rheumatology Association (IRA); is one of the manifestations that indicate the degree of activity of the LES disease, with the presence of

Table 1
Sample characteristics.

Group	n	%	Mean Age	Std. Deviation	p
SLE patients with cutaneous vasculitis	29	53,7	29,6	7,6	0,887
SLE patients without cutaneous vasculitis	25	46,3	29,9	9,5	

Table 2
Distribution of gender by group.

Gender		Group		Total
		SLE patients with cutaneous vasculitis	SLE patients without cutaneous vasculitis	
Male	n	1	2	3
	%	3,4%	8,0%	5,6%
Female	n	28	23	51
	%	96,6%	92,0%	94,4%
Total	n	29	25	54
	%	100,0%	100,0%	100,0%

Chi Square test (p = 0.467)

Table 3
Distribution of skin manifestations

Skin manifestations	n	%
Erythema	1	3,4
Erythema, necrosis	1	3,4
Erythema, petechiae	1	3,4
Necrosis	3	10,3
Papules	1	3,4
Papules, necrosis	7	24,1
Papules, pustules	1	3,4
Papules, pustules, petechiae	1	3,4
Petechiae	8	27,6
Petechiae, purpura, papules	4	13,8
Purpura, petechie	1	3,4
Total	29	100,0

Table 4
Correlation between anti-dsDNA IgA and cutaneous vasculitis in SLE.

anti-dsDNA IgA		Group		Total
		SLE with cutaneous vasculitis	SLE without cutaneous vasculitis	
Positive	n	29	18	47
	%	100,0%	72,0%	87,0%
Negative	n	0	7	7
	%	0,0%	28,0%	13,0%
Total	n	29	25	54
	%	100,0%	100,0%	100,0%

Chi Square test (p = 0.002)

cutaneous vasculitis < 18% of the skin surface, it is said to be moderately active (6–10).[13]

Cutaneous small vessel vasculitis (SVV) is the most common non-specific skin manifestation in SLE patients, occurring in 20% of cases. In SVV, there are punctate lesions, palpable purpura, ulcers, plaques or erythematous macules, and erythema with new or recurrent necrosis.[14] One form of SVV is urticarial vasculitis which is known to be associated with Immunoglobulin A.[18]

Anti-dsDNA antibody levels were found to be positive in 37–98% of SLE subjects. Anti-dsDNA binds to antigens such as histones, DNA, ribosomes, adenylyl-cyclase protein, profilin II, fibronectin and b2- glycoprotein. When inflammation occurs, monocytes respond to it, then attract and release cytokines, causing a local increase in inflammation within the vascular endothelium and ultimately increasing the sensitivity of anti-dsDNA antibodies. The risk factor for the degree of disease activity was associated with the presence of cutaneous vasculitis.[11]

This study showed a significant relationship between anti-dsDNA IgA levels and the severity of SLE and cutaneous vasculitis ($p > 0.05$). This is supported by Kallas et al., who found no association between hypocomplementemia or anti-dsDNA and cutaneous vasculitis. Hypocomplementemia and high disease activity have been reported to be associated with cutaneous vasculitis. Found no association between hypocomplementemia or anti-dsDNA and cutaneous vasculitis.[15] Similarly, Drenkard et al. observed both cutaneous vasculitis and visceral vasculitis, patients with visceral but not cutaneous vasculitis had higher mortality than patients without cutaneous vasculitis.[19] Tseng et al., in 45 SLE patients with cutaneous vasculitis (4 males and 41 females) who met the criteria, with a mean age of 38.4 ± 13.6 years and a mean duration of disease 56.8 ± 63. At 0 months, patients with active lupus had a higher SLE Disease Activity Index ($p < 0.0001$), shorter SLE duration ($p = 0.033$), higher levels of anti-dsDNA antibodies ($p = 0.018$) and C3 levels. lower levels ($p = 0.042$).[20] Miltenburg et al. concluded that elevated levels of IgA anti-ds-DNA antibodies play a role in disease activity with joint and kidney involvement.[21]

Table 5
The correlation of Mex-Sledai with cutaneous vasculitis in SLE.

MEX-SLEDAI		Group		Total
		SLE with cutaneous vasculitis	SLE without cutaneous vasculitis	
Mild	n	0	9	9
	%	0,0%	36,0%	16,7%
Moderate	n	11	5	16
	%	37,9%	20,0%	29,6%
Severe	n	14	11	25
	%	48,3%	44,0%	46,3%
Very Severe	n	4	0	4
	%	13,8%	0,0%	7,4%
Total	n	29	25	54
	%	100,0%	100,0%	100,0%

Chi Square test (p = 0.002)

Table 6
The correlation between Mex-Sledai and anti-dsDNA IgA

MEX-SLEDAI		anti-dsDNA IgA		Total
		Positive	Negative	
Mild	n	4	5	9
	%	8,5%	71,4%	16,7%
Moderate	n	15	1	16
	%	31,9%	14,3%	29,6%
Severe	n	24	1	25
	%	51,1%	14,3%	46,3%
Very Severe	n	4	0	4
	%	8,5%	0,0%	7,4%
Total	n	47	7	54
	%	100,0%	100,0%	100,0%

Chi Square test (p = 0.001)

However, there are several recommendations to further research related to this topic. Firstly, the correlation between cutaneous vasculitis and disease severity and IgA anti-dsDNA levels in SLE patients needs to be verified in a larger population. Studies with different antibody phenotypes such as IgM, antinucleosome IgG and complement are recommended. Furthermore, histopathological biopsy that gives further information and the differences in each grade of vasculitis is needed.

Conclusion

Based on the findings of this study, it can be concluded that the level of anti-dsDNA IgA is associated to the severity of disease in systemic lupus erythematosus (SLE) patients with cutaneous vasculitis, implying that the anti-dsDNA IgA level and the presence of cutaneous vasculitis can be used as predictors of disease severity in SLE patients.

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