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ORIGINAL ARTICLE

Evaluation of systemic lupus erythematosus disease activity using anti-α-enolase antibody and RDW

Yunxiu Huang[1] · Linmu Chen[2] · Baofang Zhu[1] · Hui Han[1] · Yanfang Hou[1] · Weijia Wang[1]

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Abstract

The objective of the study was to investigate the value of anti-α-enolase antibody (Ab) combined with RDW in evaluating the activity of systemic lupus erythematosus (SLE). Levels of serum anti-α-enolase Ab and RDW were detected in 193 SLE patients and 98 healthy controls by ELISA and automatic blood cell counter (XN9000), respectively. Furthermore, the correlation between anti-α-enolase Ab and RDW in evaluating the activity of SLE was evaluated by correlation analysis. The level of anti-α-enolase Ab (9.16 ± 0.44 ng/mL in stable group and 10.26 ± 0.36 ng/mL in activity group) was significantly higher than that in the healthy control (7.05 ± 0.27 ng/mL). The level of RDW (12.92% ± 1.23% in stable group and 13.57% ± 2.12% in activity group) was significantly higher than that in the healthy control (12.46% ± 0.61%). The levels of anti-α-enolase Ab or RDW in SLE patients were positively correlated with SLEDAI-2 K score ($r = 0.75$, $r = 0.73$), respectively. Compared with the anti-α-enolase Ab (AUC: 78.0%) or RDW (AUC:80.0%) alone, anti-α-enolase Ab combined with RDW (AUC: 81.0%) had the best of the effectiveness of evaluating activity of SLE. These data suggested that combined anti-α-enolase Ab with RDW might be good biomarker to predict the activity of SLE in clinical.

Keywords Anti-α-enolase antibody · RDW · Systemic lupus erythematosus · Disease activity

Abbreviations

SLE	Systemic lupus erythematosus
SLEDAI-2 K	Disease activity index 2000
AIDS	Autoimmune diseases
MCV	Mean corpuscular volume
RDW	Red blood cell distribution width
RBC	Red blood cell
HGB	Hemoglobin
C3	Complement 3
C4	Complement 4
ASO	Anti-streptolysin O
RF	Rheumatoid factor
NETs	Extracellular trappings

Introduction

SLE is a kind of autoimmune diseases involving multiple organs in young women commonly [1, 2]. Its hematology change is often the starting clinical symptoms of SLE. Red blood cell distribution width (RDW) is a routine parameter that reflects size variations in erythrocytes [3]. Recently, Amparo et al. have showed that baseline level of RDW is an easily available parameter not only capable of reflecting SLE overall activity, but also predicting therapeutic outcomes and the risk of disease flare irrespective of anemia status [4]. They demonstrated that RDW may be a useful index to estimate the disease activity of SLE [5, 6]. High RDW has been associated with cardiovascular events, inflammatory diseases and autoimmune diseases [7]. But RDW could be a useful index for disease activity assessment for SLE patients without hematological complications. So, a more specific indicator to evaluate the activity of SLE is needed urgently.

The chronic inflammatory process, which is triggered by auto-antigen and maintained by both environmental and genetic factors, is a common characteristic for all autoimmune diseases [8]. The inflammatory components often involved in the autoimmune diseases [9]. Alpha-enolase(α-enolase), also called non-neuronal enolase, belongs to a family of cytoplasmic and glycolytic enzymes, which

✉ Weijia Wang
wwj0760@163.com

[1] Department of Laboratory Medicine, Zhongshan Hospital of Sun Yat-Sen University, 2 Sunwendong Road, Guangzhou, Guangdong Province 528403, China

[2] Department of Pharmacy, Zhongshan Hospital of Sun Yat-Sen University, Guangzhou, Guangdong Province 528403, China

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exerts many other functions in eukaryotes and prokaryotes [10]. A-enolase is a component of the complex extracellular trappings (NETs) which are released by neutrophils via an active process coined NETosis [11]. Antibodies (Abs) against α-enolase have been detected in a large variety of infectious and autoimmune diseases, such as SLE [12]. Some recent studies have also shown that anti-α-enolase Ab was increased in patients with autoimmune diseases, such as inflammatory bowel disease, SLE, rheumatoid arthritis (RA), Bechet's disease, Alzheimer's disease or psoriasis [13–16]. Bruschi et al. showed that a multiantibody composition in LN, where IgG2 autoantibodies against a-enolase and annexin AI predominate in the glomerulus and can be detected in serum [17]. Besides, they also demonstrated that timely autoantibody characterization might allow outcome prediction and targeted therapies for patients with nephritis by investigating glomerular autoantibodies recognizing planted antigens from laser-microdissected renal biopsy samples of 20 patients with LN [18]. However, the value of anti-α-enolase Ab in assessing the disease activity of SLE has not been fully elucidated.

In this study, we retrospectively analyzed the medical records of 193 SLE patients (80 stable SLE patients and 113 activity SLE patients) and 98 healthy controls. The relationship between RDW, anti-α-enolase Ab and SLE Disease Activity Index 2000 (SLEDAI-2 K) [19] was evaluated. Our data suggested that combined anti-α-enolase Ab with RDW might be a good biomarker to predict activity of SLE in clinical.

Materials and methods

Participants

From February 2019 to February 2019, the medical records of 193 untreated SLE patients (10 males and 183 females) were collected in Sun Yat-sen University affiliated Zhongshan Hospital. All SLE patients in this study were divided into stable group (SLEDAI-2 K scores < 10) and activity group (SLEDAI-2 K scores > 10). Clinical and laboratory data from 193 SLE patients and 98 healthy individuals required to assess disease activity at the time of blood sampling were recorded and the serum was immediately frozen at -80℃ to assay the level of Abs within one month. Informed consent was obtained from all individual participants. SLE patients were excluded if they had one of the following combined diseases/situations: (1) other autoimmune disease, such as Sjogren Syndrome (SS), RA and IBD; (2) malignant diseases; (3) end stage of renal disease; (4) liver disease such as hepatitis and liver cirrhosis, since RDW can be greatly affected by liver disease [20]; (5) hematology disease or received blood transfusion during the past 4 months. The diagnosis of SLE was based on the criteria established by the American College of Rheumatology (ACR) [21]. The control group included 98 healthy individuals that visited the hospital for routine checkup.

Data extraction

Clinical characteristics and laboratory test results of all enrolled subjects were extracted from the medical records. In addition, SLE Disease Activity Index 2000 (SLEDAI-2 K) [19] was calculated according to medical records for each patient by two independent rheumatologists.

ELISA

The sera obtained from 193 SLE patients and 98 healthy controls were subjected to ELISA, according to the manufacturer's instructions (Cat. #JL46123, Jiang's biological, China).

Statistics

Continuous variables were displayed as mean ± standard deviation and compared by Student's t test or Mann–Whitney U test. The Spearman approach was used to analyze the correlation between two continuous variables. All the statistical analyses were performed in SPSS 19.0 and GraphPad Prism 8.0. $p < 0.05$ was determined as significant.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Board of the Sun Yat-sen University affiliated Zhongshan Hospital. This study had no influence on the subsequent management of patients.

Results

Clinical characteristics of the participants

Clinical characteristics of the 193 patients and 98 healthy controls used in this study are shown in Table 1. There was no difference between the two groups in age and gender. However, the differences between the two groups in C3, C4, and anti-dsDNA antibodies reflected the disease activity.

Levels of anti-α-enolase antibody and RDW were increased in SLE patients

RDW is a useful indicator of disease activity and response to therapy in SLE [6].

Table 1 Characteristics of participants

Parameters	SLE patients		Healthy controls		*p*
	NO	Results	NO	Results	
Age(y)	193	37.19 ± 12.01	98	39.35 ± 10.09	NS
Gender(male/female)	193	10/183	98	20/78	NS
RBC (10^{12}/L)	193	4.12 ± 0.51	98	4.38 ± 0.42	0.011
HGB (g/L)	193	118.26 ± 20.06	98	136.09 ± 13.21	0.002
MCH (pg)	193	28.40 ± 3.06	98	29.65 ± 2.05	0.018
RDW (%)	193	13.89 ± 2.50	98	12.46 ± 0.61	0.001
MCHC (g/L)	193	314.03 ± 32.05	98	329.04 ± 7.20	0.002
D-Dimer (mg/L)	193	1.68 ± 2.07	98	0.35 ± 0.07	0.002
C3 (g/L)	193	0.82 ± 0.26	98	1.19 ± 0.17	0.001
C4 (g/L)	193	0.17 ± 0.02	98	0.29 ± 0.06	0.001
IgA (g/L)	193	2.82 ± 1.07	98	2.31 ± 0.72	0.092
IgG (g/L)	193	12.56 ± 5.42	98	11.41 ± 1.90	0.008
IgM (g/L)	193	1.02 ± 0.52	98	1.20 ± 0.51	0.177
ASO (U/mL)	193	52.65 ± 57.12	–	–	–
RF (U/mL)	193	31.66 ± 130.86	–	–	–
Anti-α-enolase Ab (mg/L) Ab (ng/mL)	193	9.67 ± 0.68	98	7.05 ± 0.27	0.001
SLEDAI-2 K score	193	9.52 ± 4.05	–	–	–

The levels of RDW in patients with SLE (13.89% ± 2.50%) were significantly higher than those in the healthy control group (12.46% ± 0.61%). More important, the levels of RDW in stable group (12.92% ± 1.23%) were significantly higher than those in the activity group (13.57% ± 2.12%, $p = 0.001$). It indicated that the levels of RDW are association with the activity of SLE (Fig. 1a). To evaluate the value of anti-α-enolase Ab, we test the levels of anti-α-enolase Ab in three groups by ELISA. Our study showed that the levels of anti-α-enolase Ab in patients with SLE (9.67 ± 0.68 ng/mL) were significantly higher than those in the healthy control group (7.05 ± 0.27 ng/mL). With the increasing activity of SLE, the levels of anti-α-enolase Ab in the activity group (10.26 ± 0.36 ng/mL) were significantly higher than those in stable group (9.16 ± 0.44 ng/mL, $p = 0.001$) (Fig. 1b).

Serum anti-α-enolase Ab level has correlations with the activity of SLE

The Spearman approach was used to estimate the correlation between SLEDAI-2 K scores and anti-α-enolase Ab level or RDW. Hu et al. demonstrated that RDW is a potential index to assess the disease activity of SLE [6]. Our results showed that anti-α-enolase Ab ($r = 0.74$) (Fig. 2a) has the same correlation with SLEDAI-2 K scores compared with RDW ($r = 0.78$) (Fig. 2b). Moreover, anti-α-enolase Ab was positively correlated with serum IgM (Fig. 2c) ($r = 0.46$) and ESR ($r = 0.69$) (Fig. 2d). However, the correlation between anti-α-enolase Ab and serum IgA, IgG, C3, C4, anti-dsDNA antibody, anti-nucleosome antibody and anti-histone antibody was not statistically significant (data not shown).

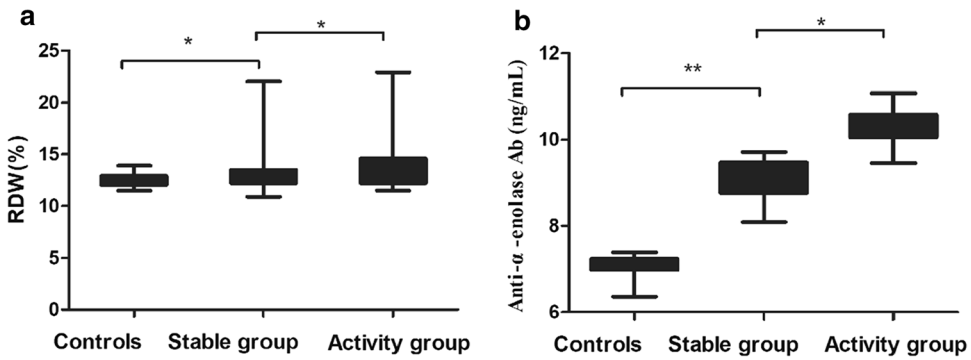

Fig. 1 Levels of anti-α-enolase Ab in SLE patients and healthy controls. **a** Level of RDW in whole blood in the stable group and activity group. **b** Level of anti-α-enolase Ab in serum in the stable group and activity group. (*$p = 0.001$, **$p < 0.001$)

Table 2 Evaluating SLE activity by RDW and anti-α-enolase antibody

Parameter	AUC (95%CI)	*p* Value	Sensitivity (%)	Specificity (%)	Youden index
RDW	0.80	0.001	68.20%	91.70%	0.59
Anti-α-enolase Ab	0.78	0.001	68.20%	87.50%	0.58
RDW and anti-α-enolase Ab	0.81	0.001	81.8%	80.20%	0.61

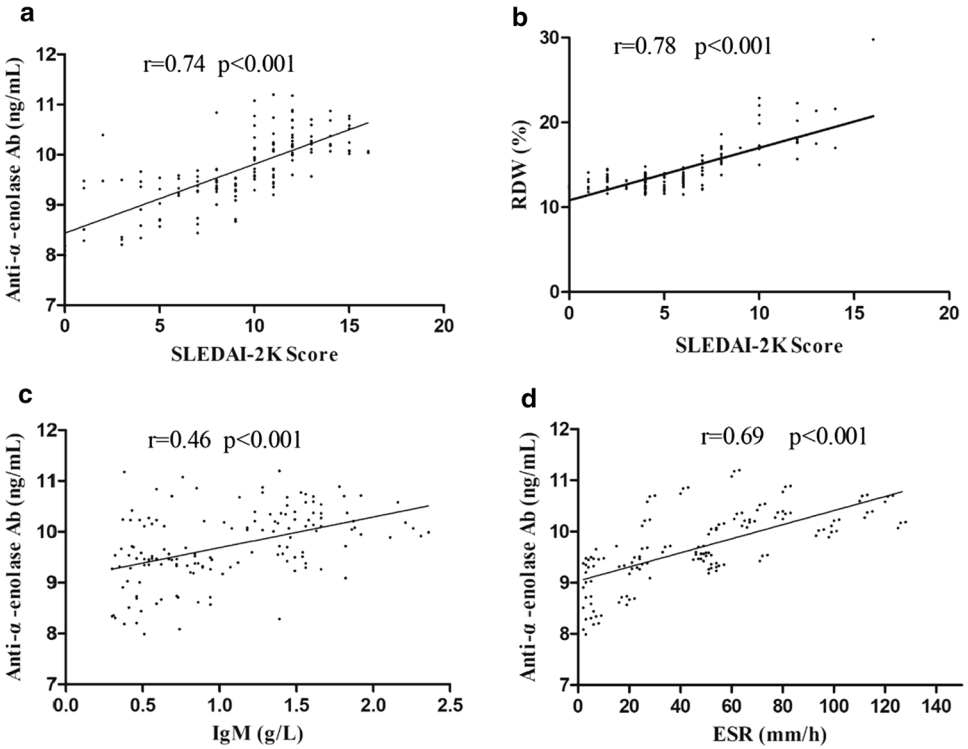

Fig. 2 Analysis of the correlations between serum anti-α-enolase Ab level and experimental parameters in SLE patients. The Spearman approach was used to estimate the correlation between anti-α-enolase Ab, RDW, SLEDAI-2 K scores, IgM and ESR. Correlation coefficient and corresponding *p* values are indicated in each scatter plot

Combination of anti-α-enolase Ab and RDW significantly improved the sensitivity of assessing SLE activity

Anti-α-enolase antibody combined with RDW was used to assess the activity of SLE. Combination of anti-α-enolase Ab and RDW assessing the activity of SLE has higher sensitivity than anti-α-enolase antibody or RDW. When the RDW or Anti-α-enolase antibody alone was used to assess the activity of SLE, the specificity was higher, but the sensitivity was too low. We found that combination of anti-α-enolase Ab and RDW, the sensitivity and specificity are optimal. Moreover, when the anti-α-enolase antibody was combined with RDW, the AUC (81.0%) was higher than that of anti-α-enolase antibody (AUC: 78.0%) or RDW (AUC:80.0%) (Fig. 3 and Table 2). These data suggested that anti-α-enolase Ab and RDW may be a potential indicator for evaluating activity of SLE.

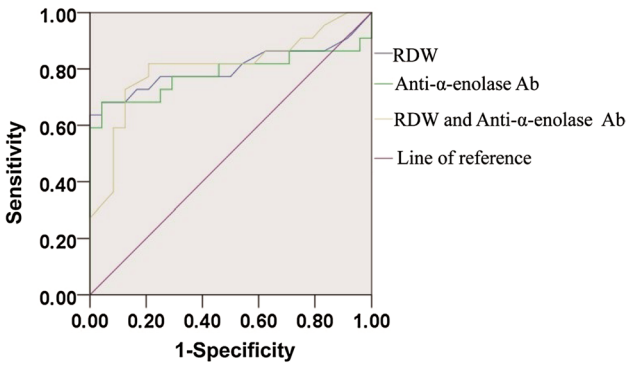

Fig. 3 Receiver operating characteristic curve for evaluating activity of SLE by anti-α-enolase antibody and RDW. Anti-α-enolase antibody evaluating the activity of SLE combined with RDW has the best assessment of the effectiveness (area under the ROC curve (AUC):81.0%) compared with only anti-α-enolase antibody (area under the ROC curve (AUC):78.0%) and RDW (area under the ROC curve (AUC):80.0%), respectively

Discussion

SLE patients are usually accompanied by anemia, and RDW often used the size of a red blood cell volume variation coefficient, which can be used to assure the patient in anemia. Studies have found that chronic inflammation and the inflammatory cytokines suppressed the mature of red blood cells by influencing erythropoietin, which leads to immature red blood cells passing into peripheral blood and the increase in RDW. They showed that SLE patients have increased RDW irrespectively of anemia status [4]. Inflammatory indexes, such as CRP and ESR, may be useful to assess the activity of autoimmune diseases as well. RDW had positive correlation with CRP, ESR and SLEDAI-2 K scores [6, 7, 14, 22].

In this study, we found that the levels of anti-α-enolase Ab and RDW in patients with SLE were significantly higher than those in the healthy control group. Furthermore, we found that the levels of anti-α-enolase Ab and RDW in activity group were significantly higher than those in the stable group. The levels of anti-α-enolase Ab and RDW in SLE patients are positively correlated with SLEDAI-2 K scores. Musca et al. found that anti-α-enolase antibodies could contribute to renal injury not only by the local formation of immune complexes, but also by direct damage to endothelial cells [12]. In our previous study, we demonstrated that anti-α-enolase Ab may be a potential indicator for the prediction of nephritis in SLE patients [22]. Lee et al. found that anti-α-enolase Ab is correlated with disease activity in RA [23]. In this study, we found that both the levels of serum anti-α-enolase Ab and RDW were higher in active SLE patients, positively correlated with SLEDAI-2 K scores.

On the other hand, we also found that anti-α-enolase antibody combined with RDW evaluating activity of SLE had the best assessment of the effectiveness (area under the ROC curve (AUC):81.0%) compared with only anti-α-enolase antibody (area under the ROC curve (AUC):78.0%) or RDW (area under the ROC curve (AUC):80.0%), respectively. These data suggested that anti-α-enolase Ab may be a potential indicator for evaluating activity of SLE. Our results suggested that anti-α-enolase Ab is correlated with disease activity, which is consistent with those findings [14, 22]. Moreover, Bae S et al. demonstrated that anti-α-enolase Abs were contributed to the perpetuation of synovial inflammation in RA by stimulating monocytes and macrophages to produce increased amounts of proinflammatory mediators, such as TNF-α, IL-1α/β, IFN-γ, and PGE2 via the p38 mitogen-activated protein kinase and NF-kB pathways [24]. Apostolidis et al. showed that cytokines were intimately involved in every step of the SLE pathogenesis [25]. Therefore, both of our and previous studies showed that inflammatory indexes, such as CRP and ESR, may be useful to assess the activity of autoimmune diseases as well, which have positive correlation with anti-α-enolase antibody and RDW. It suggested that the risk of infections may further increase the levels of anti-α-enolase antibody and RDW levels in SLE patients. Murdaca et al. demonstrated that vaccinations against flu and pneumococcal infections could protect against infections and thus the risk of SLE flares [26]. Li ZX et al. showed that a higher seroprevalence of EBV antibodies in SLE patients compared with controls by a systematic review and meta-analysis which searched the MEDLINE and EMBASE databases from 1966 to 2018 with no language restrictions [27]. Lei Zhang et al. showed that CMV infection is not rare in lupus nephritis patients and therapy consensus guideline is still lacking [28]. Therefore, the study of EBV, CMV, flu and pneumococcal vaccinations in SLE patients is essential. However, future studies are needed to search for the mechanism of the increased anti-α-enolase Ab and signal pathways. In future studies, we aim to further investigate the concrete mechanism of the increased anti-α-enolase Ab and signal pathways in SLE patients.

In conclusion, anti-α-enolase Ab combined with RDW evaluating the activity of SLE had the best assessment of the effectiveness. However, the specificity has no promotion. A larger sample included in studies will be needed to explain the correlation.

Author contributions Yunxiu Huang and Weijia Wang designed the research; Baofang Zhu and Linmu Chen analyzed the data; Hui Han and Yanfang Hou performed the ELISA assay; Yunxiu Huang wrote the paper. All authors reviewed and approved the manuscript.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest related to this study.

Ethics approval This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Board of the Sun Yat-sen University affiliated Zhongshan Hospital. This study had no influence on the subsequent management of patients.

Informed consent Informed consent was obtained from all individual participants included in the study.

Highlight The serum level of anti-a-enolase Ab was relatively higher in the activity patients. Serum anti-α-enolase Ab level has correlations

with the activity of SLE. Anti-α-enolase Ab evaluating SLE activity combined with RDW is highly effective.

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