Anna Bogaczewicz[1], Iwona Szadkowska[2], Jan Kowalski[2], Tomasz Sobów[1],
Ewa Robak[3], Jarosław Bogaczewicz[3], Anna Woźniacka[3]

The examination of the relationship between cognitive functions and cardiovascular condition in systemic lupus erythematosus patients without obvious neuropsychiatric features

Badanie zależności pomiędzy funkcjami poznawczymi oraz stanem układu sercowo-naczyniowego u chorych na toczeń rumieniowaty układowy bez objawów neuropsychiatrycznych

[1] Department of Medical Psychology, Medical University of Lodz, Poland
[2] Department of Internal Diseases and Cardiac Rehabilitation, Medical University of Lodz, Poland
[3] Department of Dermatology and Venereology, Medical University of Lodz, Poland
Correspondence: Anna Bogaczewicz, MD, PhD, Department of Medical Psychology, Medical University of Lodz, Sterlinga 5, 91-425 Lodz, Poland, tel.: +48 42 630 15 73, +48 42 632 25 94, fax: +48 42 630 15 73, e-mail: anna.bogaczewicz@umed.lodz.pl

Abstract

The aim: To investigate relations between selected neurocognitive parameters and echocardiographic variables in patients with systemic lupus erythematosus. **Material and methods:** The study included 24 female patients with systemic lupus erythematosus. In the neuropsychological assessment, the Cambridge Neuropsychological Test Automated Battery (CANTAB) was performed, using the following tests: Motor Screening Task, Big/Little Circle, Paired Associates Learning, Stockings of Cambridge and Graded Naming Test. A decrease in the cognitive function was defined as the value of results below two standard deviations. The function of the heart was examined with transthoracic echocardiography. The diastolic function of the left ventricle was estimated with the ratio of early to late ventricular filling velocities. **Results:** In 8.3% of patients, Mean Latency (Motor Screening Task) was lower than standard zero, whereas Mean Errors (Motor Screening Task) remained above the cut-off level. Paired Associates Learning, Subsequent Thinking Mean Time (Stockings of Cambridge), Problems Solved in Minimum Moves (Stockings of Cambridge) and Graded Naming Test were found to be lower than standard zero in 79.16%, 26.08%, 70.83%, and 87.5% of patients, respectively. Mean Initial Thinking Time (Stockings of Cambridge) was above the cut-off level. When the cut-off level was defined as results below two standard deviations from standard zero, a reduction in cognitive functions was found in 4% of patients in Paired Associates Learning and Graded Naming Test, and in 1% of patients in Mean Subsequent Thinking Time (Stockings of Cambridge) and Problems Solved in Minimum Moves (Stockings of Cambridge). Mean Latency (Motor Screening Task), Mean Errors (Motor Screening Task), Big/Little Circle, and Mean Initial Thinking Time (Stockings of Cambridge) remained above the cut-off level. Based on the evaluation of ejection fraction, no patient showed signs of systolic dysfunction of the left ventricle, defined as ejection fraction <55%. There was no correlation between the ejection fraction and the results obtained in those CANTAB tests which were lower than two standard deviations. The ratio of early and late ventricular filling velocities showed no correlation with the results of Paired Associates Learning, Stockings of Cambridge, and Graded Naming Test. **Conclusions:** A decrease in selected cognitive functions in patients with systemic lupus erythematosus, examined with CANTAB and demonstrated by the results of Paired Associates Learning, Graded Naming Test, Mean Subsequent Thinking Time and Problems Solved in Minimum Moves in Stockings of Cambridge, may be present without any features of the heart failure.

Key words: systemic lupus erythematosus, echocardiography variables, cognitive functions, Cambridge Neuropsychological Test Automated Battery (CANTAB)

Streszczenie

Cel: Zbadanie zależności pomiędzy poziomem wybranych funkcji poznawczych a zmiennymi echokardiograficznymi u pacjentów z toczniem rumieniowatym układowym. **Materiał i metody:** Badaniem objęto 24 pacjentki z toczniem rumieniowatym układowym. Do oceny neuropsychologicznej wykorzystano testy metody Cambridge Neuropsychological Test Automated Battery (CANTAB): Motor Screening Task, Big/Little Circle, Paired Associates Learning, Stockings

of Cambridge i Graded Naming Test. Za próg spadku poziomu funkcji poznawczych przyjęto dwa odchylenia standardowe. Funkcje serca badano przy użyciu transtorakalnej echokardiografii. Czynność rozkurczową lewej komory oceniano, wykorzystując iloraz prędkości wczesnego i późnego napływu mitralnego. **Wyniki:** U 8,3% pacjentów wynik uzyskany w Mean Latency (Motor Screening Task) był niższy niż standardowe zero, podczas gdy wynik Mean Errors (Motor Screening Task) pozostał powyżej standardowego zera. Wyniki uzyskane w testach: Paired Associates Learning, Subsequent Thinking Mean Time (Stockings of Cambridge), Problems Solved in Minimum Moves (Stockings of Cambridge) i Graded Naming Test okazały się niższe od standardowego zera odpowiednio w 79,16%, 26,08%, 70,83% i 87,5% pacjentów. Wartość Mean Initial Thinking Time (Stockings of Cambridge) była powyżej standardowego zera. Obniżenie funkcji poznawczych (dwa odchylenia poniżej standardowego zera) stwierdzono u 4% pacjentów w Paired Associates Learning oraz Graded Naming Test, a u 1% pacjentów w Subsequent Thinking Mean Time (Stockings of Cambridge) i Problems Solved in Minimum Moves (Stockings of Cambridge). Z kolei wyniki uzyskane w Mean Latency (Motor Screening Task), Mean Errors (Motor Screening Task), Big/Little Circle oraz Mean Initial Thinking Time (Stockings of Cambridge) pozostały powyżej standardowego zera. Żaden pacjent nie wykazał objawów dysfunkcji skurczowej lewej komory serca, definiowanej jako frakcja wyrzutowa <55%. Nie stwierdzono korelacji pomiędzy frakcją wyrzutową i wynikami uzyskanymi w tych badaniach CANTAB, które były niższe niż dwa odchylenia standardowe. Nie wykazano korelacji pomiędzy wczesną i późną komorową prędkością napełnień a wynikami Paired Associates Learning, Stockings of Cambridge oraz Graded Naming Test. **Wnioski:** Spadek wybranych funkcji poznawczych u pacjentów z toczniem rumieniowatym układowym badanych metodą CANTAB oraz przedstawianych w postaci wyników w testach Paired Associates Learning, Graded Naming Test, Mean Subsequent Thinking Time i Problems Solved in Minimum Moves (Stockings of Cambridge) może wystąpić bez cech niewydolności serca.

Słowa kluczowe: toczeń rumieniowaty układowy, parametry echokardiograficzne, funkcje poznawcze, Cambridge Neuropsychological Test Automated Battery (CANTAB)

INTRODUCTION

The neuropathology of cognitive impairment is diverse and includes both lesions observed in Alzheimer's disease, which are the most common, as well as lesions resulting from cerebral infarcts, Parkinson's disease and dementia with Levy's bodies (Oishi and Lyketsos, 2014; Schneider *et al.*, 2007). However, it would be an oversimplification to search for risk factors of cognitive dysfunction only among neurodegenerative disorders. Many other diseases, such as heart failure and systemic lupus erythematosus (SLE), exert adverse effects on cognitive functions (Hajduk *et al.*, 2013; Unterman *et al.*, 2011). Not all mechanisms in the pathogenesis of neuropsychiatric symptoms in SLE have been fully explained, but the most important are those related to the production of cytokines, autoantibodies and impaired blood flow (Meszaros *et al.*, 2012; Popescu and Kao, 2011; Roubey, 1998; Unterman *et al.*, 2011). Vascular damage observed in SLE is a consequence of vasculitis, thrombosis and atherosclerosis (Roubey, 1998). Atherosclerotic plaques are observed in 17–65% of patients with SLE (Doria *et al.*, 2003), and the risk of myocardial infarction in patients aged 35–44 years is 50 times higher than the risk in the control group (Manzi *et al.*, 1997). The need of searching for connections between the state of cardiovascular system and cognitive functions in SLE is therefore justified. The identification of such parameters, which exert an impact on cognitive functions, would indicate the need for their early evaluation in daily practice.

The aim of the study was to investigate the relationship between the selected neurocognitive and echocardiographic parameters in patients with SLE without neuropsychiatric lupus and without any obvious signs of heart failure.

MATERIAL AND METHODS

The study involved 24 women with SLE, aged 27–62, mean age 42.16 ± 10.12. The diagnosis of SLE was established using the classification criteria for SLE updated in 1997 (Hochberg, 1997). The duration of the disease ranged from 2 to 24 years, mean 11 ± 5.93 years. According to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the activity of the disease in the entire group of patients was less than 6 (Lam and Petri, 2005). The study was approved by the local Ethics Committee (No RNN/123/13/KB). The exclusion criteria were: the lack of cooperation of the patient, features of neuropsychiatric lupus or antiphospholipid syndrome, psychotic symptoms, the use of psychoactive substances, acute coronary disease during the last six months, the signs of heart failure and uncontrolled hypertension.

In order to perform the neuropsychological assessment, we used the computer Cambridge Neuropsychological Test Automated Battery (CANTAB), which uses non-verbal tasks displayed on the screen and requires non-verbal answers on the same touch screen. In our study, a reduction in cognitive functions was defined as results below two standard deviations (*SD*) from standard zero (Calderón *et al.*, 2014). The obtained result are standardized and expressed as the number of standard deviations deviated from the standard zero, which is an equivalent of the intended range of standards, taking into account age and sex of the subjects. Therefore, negative results indicate a failure to obtain a standardized value of the expected threshold, depending on the age and sex of the tested person. In our study, the following CANTAB tests were used:

- MOT (Motor Screening Task), which examines perception as well as speed and accuracy of movements.

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Clinical feature	The number of patients (percentage)
Malar rash	11/24 (45.8%)
Discoid rash	4/24 (16.6%)
Oral ulcers	2/24 (8.3%)
Photosensitivity	14/24 (58.3%)
Nonerosive arthritis	23/24 (95.8%)
Serositis	2/24 (8.3%)
Renal disorder	4/24 (16.4%)
History of neuropsychiatric lupus symptoms	2/24 (8.3%)
Haematologic disorder	19/24 (79.16%)
Positive antinuclear antibody	24/24 (100%)

Tab. 1. Clinical characteristics of patients with SLE

The results are expressed as delayed reaction (Mean Latency – MOT ML) and the amount of mistakes (Mean Errors – MOT ME).

- BLC (Big/Little Circle) evaluates attention, understanding and ability to learn, perform tasks and reverse tasks. The results are expressed as a percentage of correct reactions.
- PAL (Paired Associates Learning) is used to study short-term visual memory and learning. The results demonstrate the number of mistakes made by the participant (Errors-PAL).
- SOC (Stockings of Cambridge) assesses cognitive planning, anticipation and decision-making. The results are expressed as the time of initiation (SOC Mean Initial Thinking Time – SOC MITT), time of execution (SOC Mean Subsequent Thinking Time – SOC MSTT) and the number of made attempts (SOC Problems Solved in Minimum Moves – SOC PSMM).
- GNT (Graded Naming Test) is a test of lexical memory and the ability to name objects. The results show the percentage of correct answers.

Transthoracic echocardiography was performed with Acuson CV70 (Siemens). The following echocardiographic parameters were studied: left ventricular ejection fraction (EF) according to the modified Simpson's rule, systolic dysfunction of the left ventricle defined as EF<55%, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial diameter (LA), right ventricle diameter (RV), tricuspid annular peak systolic excursion (TAPSE), right atrial diameter (RA), aorta diameter (Ao), intraventricular septum diastolic diameter (IVSDD), posterior wall diastolic diameter (PVSDD), the ratio of the early (E) and late (A) ventricular filling velocities (E/A).

In the statistical analysis, Statistica version 10 was used. The Shapiro–Wilk test demonstrated that the analysed variables did not meet the characteristics of a normal distribution, and therefore median values as well as upper and lower quartiles were presented in descriptive statistics. To evaluate the correlation between two variables, the Spearman rank correlation coefficient was used. In all measurements, $p < 0.05$ was regarded as statistically significant.

RESULTS

The clinical characteristics of patients with SLE are shown in Tab. 1.

Results of CANTAB tests obtained by patients with SLE are presented in Tab. 2.

The percentage of patients with SLE who obtained CANTAB results below the standard zero is shown in Fig. 1.

In 8.3% of SLE patients, MOT ML was lower than standard zero, whereas MOT ME remained above the cut-off level. PAL, SOC MSTT, SOC PSMM and GNT were found to be lower than standard zero in 79.16%, 26.08%, 70.83%, and 87.5% of patients, respectively. SOC MITT was above the cut-off level. The percentage of patients with SLE who obtained results below two standard deviations from standard zero is shown in Fig. 2. When the cut-off level was defined as results below two standard deviations from standard zero, a reduction in cognitive functions was found in 4% of patients in PAL and GNT, and in 1% of patients in SOC MSTT and SOC PSMM. MOT ML, MOT ME, BLC, and SOC MITT remained above the cut-off level.

The results of transthoracic echocardiography in patients with SLE are shown in Tab. 3.

Based on the evaluation of EF, no patient showed signs of systolic dysfunction of the left ventricle, defined

CANTAB test	Median	Minimum	Maximum	Quartile	
				Upper	Lower
MOT Mean Latency (MOT ML)	1.03	−0.36	1.77	0.83	1.24
MOT Mean Error (MOT ME)	0.41	0.16	1.35	0.30	0.49
BLC [correct %]	0.16	0.15	0.18	0.16	0.18
PAL [number of errors]	−0.73	−9.61	6.40	−1.28	−0.14
SOC Mean Initial Thinking Time (SOC MITT)	0.95	0.25	1.48	0.52	1.11
SOC Mean Subsequent Thinking Time (SOC MSTT)	0.62	−2.77	1.20	−0.14	1.09
SOC Problems Solved in Minimum Moves (SOC PSMM)	−0.56	−2.11	1.12	−1.38	0.25
GNT [correct %]	−0.94	−2.70	0.63	−1.68	−0.56

Tab. 2. Results of CANTAB tests obtained by patients with SLE

Fig. 1. The percentage of patients with SLE who obtained CANTAB results below the standard zero
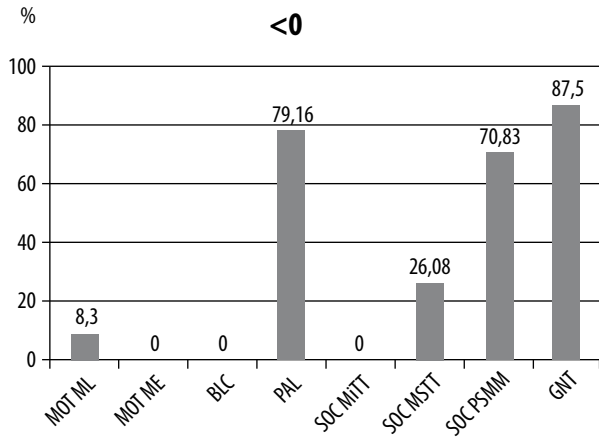

Fig. 2. The percentage of patients with SLE who obtained results below two SD from the standard zero

as EF<55%. There was no correlation between EF and the results obtained in those CANTAB tests which were lower than two standard deviations, namely PAL, SOC, and GNT. The ratio of the early (E) and late (A) ventricular filling velocities (E/A) showed no correlation with CANTAB results of PAL, SOC, and GNT.

DISCUSSION

Cognitive disorders represent a clinical problem in SLE, and in a recent meta-analysis they were found to affect 19.7% of SLE patients (Unterman *et al.*, 2011).

In our study performed in a small group of patients with SLE, a decrease in cognitive functions was revealed to a lesser extent. When the cut-off level was defined as results below two standard deviations from standard zero, a decrease was found only in 4% of patients in PAL and GNT, and in 1% of patients in SOC MSTT and SOC PSMM. However, it should be emphasised that our study was not focused on the estimation of the prevalence of cognitive impairment, and therefore it was not a cross-sectional study.
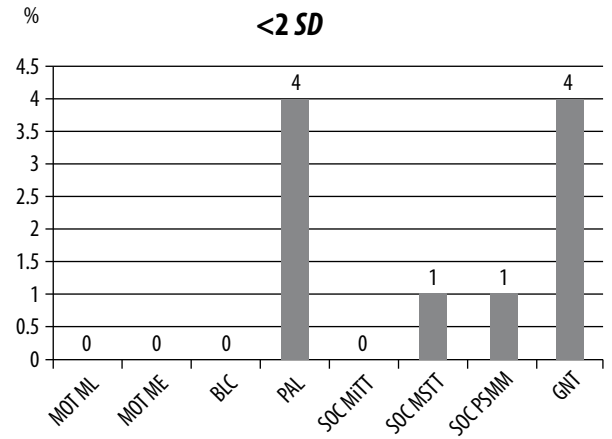
Our intention was to correlate those variables, which feature selected cognitive functions, with echocardiographic parameters. The aim appears to be justified because the pathogenesis of cognitive disorders in SLE is multifactorial and includes not only autoantibody production, immune complex deposition, cytotoxic neuronal damage and production of inflammatory mediators, but also vascular disorders and thrombosis (Meszaros *et al.*, 2012; Popescu and Kao, 2011; Roubey, 1998). In addition, the cardiovascular status was found to influence cognitive functions, as it was confirmed by a report of higher risk of cognitive impairment in patients with heart failure (Vogels *et al.*, 2007). Hence, there is a need to examine the relationship between cognitive functions and cardiovascular condition in SLE patients without obvious neuropsychiatric features. Echocardiography facilitates the identification of anomalies in echocardiographic parameters, despite the lack of developed clinical symptoms of heart disease (Cervera *et al.*, 1992). Therefore, transthoracic echocardiography is recommended for the evaluation of abnormalities of the heart structures in patients with autoimmune connective

Parameter [reference range]	Median	Minimum	Maximum	Quartile	
				Lower	Upper
EF (ejection fraction; %) [≥55%]	62.0	58.0	63.0	61.0	63.0
LVEDD [≤50 mm]	46.0	40.0	58.0	45.0	49.0
LVESD v[≤35 mm]	27.0	20.0	39.0	24.0	28.5
LA [≤40 mm]	31.5	26.0	40.0	28.5	33.0
RV [≤30 mm]	22.0	17.0	29.0	20.5	24.0
TAPSE [>15 mm]	26.0	22.0	34.0	25.0	28.0
RA [≤50 mm]	43.5	38.0	50.0	41.5	48.0
Ao [≤40 mm]	30.0	25.0	41.0	28.0	33.0
IVSDD [≤12 mm]	9.0	8.0	12.0	9.0	10.0
PVSDD [≤12 mm]	9.0	8.0	11.0	9.0	9.0
E/A	1.17	0.55	2.0	0.92	1.41

Tab. 3. Results of transthoracic echocardiography in patients with SLE

tissue diseases (Turiel *et al.*, 2005). The incidence of cardiac abnormalities in patients with SLE is about 50% (Cervera *et al.*, 1992). Although there are differences in the incidence of specific disorders reported by various authors, the most frequent conditions are pericarditis, occurring in 11–54% of patients with SLE, valve abnormality in 40–50%, and myocarditis in 7–10% of patients (Doria *et al.*, 2003). In our study, we tried to correlate neurocognitive and echocardiographic parameters in patients without neuropsychiatric lupus or overt heart failure. To assess cognitive functions, we used a computer set, namely CANTAB. So far in SLE patients, there was only one study based on tests using CANTAB, which was performed in the Chilean population (Calderón *et al.*, 2014). This study did not show the influence of SLE on test results in screening tests, such as MOT and BLC (Calderón *et al.*, 2014). In our study, we found that 8% of patients manifested negative values in MOT. However, none of them fulfilled the criteria of cognitive impairment defined as <2 standard deviations in MOT. Our results are in accordance with those of Calderón *et al.* (2014), who did not find significant impact of SLE on cognitive functions screened by MOT. Due to the fact that in our study the results falling below 2 standard deviations concerned only PAL, GNT and SOC, the next step was to determine whether there is a correlation between these variables and echocardiographic parameters of the left ventricle, namely ejection fraction (EF) and the diastolic function of the heart, assessed by the ratio of the early (E) and late (A) ventricular filling velocities (E/A). Since exclusion criteria included the signs of heart failure, on the evaluation of the EF no patient showed signs of systolic dysfunction of the left ventricle, defined as EF<55%, and EF was not correlated with PAL, GNT and SOC. In order to examine features of right ventricular systolic dysfunction, we assessed the ratio of the early (E) and late (A) ventricular filling velocities (E/A). Features of right ventricular systolic dysfunction were not presented by any patient. We did not find any correlation between PAL, GNT, SOC and E/A. Therefore, it can be concluded that a reduction of cognitive functions in patients with SLE may occur despite the lack of features of heart failure. Such a conclusion confirms the multifactorial pathogenesis of cognitive disorders in SLE. However, there is a need for further analyses of the relationship between echocardiographic parameters of the left and right ventricles and neurocognitive functions in patients with SLE. The E/A parameter describes the characteristics of the filling of the left ventricle only approximately and this feature alone does not constitute a diagnosis of diastolic dysfunction. It seems that a more appropriate method of diastolic dysfunction assessment is the estimation of the ratio between early mitral inflow velocity and early diastolic mitral annular velocity (E/E') (Shang *et al.*, 2012). This parameter enables the identification of diastolic dysfunction of the left ventricle despite preserved ejection fraction (Shang *et al.*, 2012). A limitation of our study is certainly no assessment of E/E'. Despite

this, and despite the fact that we have found no correlations between PAL, GNT, SOC and EF, and between PAL, GNT, SOC and E/A, the relationship between heart failure and cognitive function exists. This is confirmed by a systematic review of Hajduk *et al.* (2013), who point out that there is increased risk of decreased cognitive function in patients with heart failure. Interestingly, in patients with SLE, Calderón *et al.* (2014) found reduced results in memory tests, new learning tests and cognitive planning tests (PAL, SOC). Unfortunately, the authors did not test the relationship between cognitive functions and heart failure. The importance of results of PAL and GNT was demonstrated by Blackwell *et al.* (2004), who demonstrated that these two tests in combination appear to be highly accurate in detecting cognitive dysfunction characteristic of preclinical Alzheimer's disease. The use of these tests is therefore justified even for diagnosis of diseases other than Alzheimer's disease. Also, there is a need for further studies in larger groups of patients with SLE. In addition, these studies should include assessment of both cognitive parameters and results of echocardiography. Shang *et al.* (2012) showed a relationship between the severity of SLE indicated by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) and the development of diastolic dysfunction. On the other hand, there are reports of cardiovascular disorders despite low rates of rheumatic organ damage in SLE (Palmieri *et al.*, 2009). In addition, Redfield *et al.* (2003) showed that heart diastolic dysfunction is associated with increased mortality. With no doubt, a cardiovascular disease resulting from atherosclerosis is an important clinical problem in patients with SLE and contributes to late morbidity and mortality in these patients (Aranow and Ginzler, 2000). The development of atherosclerosis in SLE results from both inflammation and dyslipidaemia (Doria *et al.*, 2003). Dyslipidaemia in SLE patients, named as lupus model dyslipoproteinaemia, features decreased HDL cholesterol, increased triglyceride levels and normal or increased levels of LDL cholesterol (Frostegård, 2005). Therefore, counteracting risk factors of atherosclerosis, both those traditional and specific for SLE, is beneficial and may indirectly lead to the improvement of cognitive functions. Our study indicates that a decrease in selected cognitive functions in patients with SLE examined with CANTAB and demonstrated by the results of PAL, GNT, SOC MSTT and SOC PSMM may be present without any features of heart failure. However, there is a need for prospective studies on the prevention of cardiovascular diseases and its influence on cognitive functions in patients with SLE.

Conflict of interest
None declared.

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References

Aranow C, Ginzler EM: Epidemiology of cardiovascular disease in systemic lupus erythematosus. Lupus 2000; 9: 166–169.

Blackwell AD, Sahakian BJ, Vesey R et al.: Detecting dementia: novel neuropsychological markers of preclinical Alzheimer's disease. Dement Geriatr Cogn Disord 2004; 17: 42–48.

Calderón J, Flores P, Babul M et al.: Systemic lupus erythematosus impairs memory cognitive tests not affected by depression. Lupus 2014; 23: 1042–1053.

Cervera R, Font J, Paré C et al.: Cardiac disease in systemic lupus erythematosus: prospective study of 70 patients. Ann Rheum Dis 1992; 51: 156–159.

Doria A, Shoenfeld Y, Wu R et al.: Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. Ann Rheum Dis 2003; 62: 1071–1077.

Frostegård J: SLE, atherosclerosis and cardiovascular disease. J Intern Med 2005; 257: 485–495.

Hajduk AM, Kiefe CI, Person SD et al.: Cognitive change in heart failure: a systematic review. Circ Cardiovasc Qual Outcomes 2013; 6: 451–460.

Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40: 1725.

Lam GK, Petri M: Assessment of systemic lupus erythematosus. Clin Exp Rheumatol 2005; 23 (Suppl 39): S120–S132.

Manzi S, Meilahn EN, Rairie JE et al.: Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol 1997; 145: 408–415.

Meszaros ZS, Perl A, Faraone SV: Psychiatric symptoms in systemic lupus erythematosus: a systematic review. J Clin Psychiatry 2012; 73: 993–1001.

Oishi K, Lyketsos CG: Alzheimer's disease and the fornix. Front Aging Neurosci 2014; 6: 241.

Palmieri V, Migliaresi P, Orefice M et al.: High prevalence of subclinical cardiovascular abnormalities in patients with systemic lupus erythematosus in spite of a very low clinical damage index. Nutr Metab Cardiovasc Dis 2009; 19: 234–240.

Popescu A, Kao AH: Neuropsychiatric systemic lupus erythematosus. Curr Neuropharmacol 2011; 9: 449–457.

Redfield MM, Jacobsen SJ, Burnett JC Jr et al.: Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003; 289: 194–202.

Roubey RA: Mechanisms of autoantibody-mediated thrombosis. Lupus 1998; 7 Suppl 2: S114–S119.

Schneider JA, Arvanitakis Z, Bang W et al.: Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007; 69: 2197–2204.

Shang Q, Yip GW, Tam LS et al.: SLICC/ACR damage index independently associated with left ventricular diastolic dysfunction in patients with systemic lupus erythematosus. Lupus 2012; 21: 1057–1062.

Turiel M, Peretti R, Sarzi-Puttini P et al.: Cardiac imaging techniques in systemic autoimmune diseases. Lupus 2005; 14: 727–731.

Unterman A, Nolte JE, Boaz M et al.: Neuropsychiatric syndromes in systemic lupus erythematosus: a meta-analysis. Semin Arthritis Rheum 2011; 41: 1–11.

Vogels RL, Scheltens P, Schroeder-Tanka JM et al.: Cognitive impairment in heart failure: a systematic review of the literature. Eur J Heart Fail 2007; 9: 440–449.

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