Cambridge Neuropsychological Test Automated Battery in assessment of cognitive parameters in patients with systemic lupus erythematosus in relation to autoantibody profile

Anna Bogaczewicz[1], Tomasz Sobow[1], Jan Kowalski[2], Jakub Ząbek[3], Anna Woźniacka[4], Jaroslaw Bogaczewicz[4]

[1]Department of Medical Psychology, Medical University of Lodz, Poland
[2]Department of Internal Diseases and Cardiological Rehabilitation, Medical University of Lodz, Poland
[3]Unit of Microbiology and Serology, Institute of Rheumatology, Warsaw, Poland
[4]Department of Dermatology and Venereology, Medical University of Lodz, Poland

Abstract

Objectives: To relate the cognitive parameters of systemic lupus erythematosus (SLE) patients in remission to their profile of autoantibodies.

Material and methods: The study included 32 patients with SLE in remission, with mild disease activity as indicated by SELENA-SLEDAI < 6. For neuropsychological assessment, the Cambridge Neuropsychological Test Automated Battery (CANTAB) was applied, using motor screening (MOT), big little circle (BLC), paired associated learning (PAL), stockings of Cambridge (SOC), and graded naming tests (GNT). Detection of autoantibodies against dsDNA, nucleosome (aNuc), Sm, and anti-cardiolipin (aCL: IgG and IgM) was performed with immunoassays.

Results: The SLE patients demonstrated standard scores below norms, matched according to age and gender, in the following tests: GNT (–0.87 ±0.85), SOC PSMM (–0.47 ±0.97), PAL (–1.88 ±3.58), and BLC (–0.31 ±1.90). GNT scores under –0.5 were found significantly more frequently in SLE patients, seen in roughly 66% of test subjects. Values for PAL and mean subsequent thinking time of stockings of Cambridge (SOC MSTT) were found to be lower than –0.5 in approximately half of the patients. Mean error of motor screening (MOT ME) was found to negatively correlate with mean latency of motor screening (MOT ML) ($r = -0.55$). PAL significantly correlated with SOC MSTT ($r = 0.38$) and with GNT ($r = 0.36$). Anti-dsDNA antibody level correlated negatively with MOT ME ($r = -0.46$). Anti-Nuc antibodies correlated with MOT ML ($r = 0.41$) but negatively correlated with MOT ME ($r = -0.58$). The levels of anti-Sm, anti-CL IgM and IgG did not correlate significantly with the outcomes of CANTAB. The age of the patients correlated negatively with MOT ME ($r = -0.36$), positively with BLC ($r = 0.53$) and negatively with SOC MSTT ($r = -0.43$). The level of anti-Nuc antibodies correlated with anti-dsDNA level ($r = 0.62$) and of anti-CL IgM with anti-Sm ($r = 0.39$) and anti-CL IgG ($r = 0.87$).

Conclusions: CANTAB reveals a decrease in selected cognitive functions in patients with SLE. ACL IgG and anti-dsDNA antibodies indicated SLE patients prone to develop a decrease in cognitive functions.

Key words: cognitive functions, systemic lupus erythematosus, neuropsychological test, autoantibodies.

Introduction

Several attempts have been made to diagnose and classify specific manifestations of neuropsychiatric systemic lupus erythematosus (NPSLE). However, during the past decades numerous criteria have been found to be insufficient in clinical practice. In 1999, the American College of Rheumatology (ACR) Research Committee introduced diagnostic criteria for 19 NPSLE syndromes [1]. In consequence, a much broader spectrum of disorders than only seizures and psychosis may be regarded as indications according to ACR diagnostic criteria [2]. However, limitations of the new neuropsychiatric criteria, as well as newer revisions, are still being revealed. The establishment of an effective diagnostic protocol is of clinical importance, since NPSLE is not a rare problem. In a recent meta-analysis, neuropsychiatric syndromes in SLE affect 56.3% of patients, while headaches affect 28.3%, mood disorders 20.7%, cognitive dysfunction 19.7%, seizures 9.9%, and cerebrovascular disease 8.0% [3]. In our previous study neurological syndromes were found in 77.27% of the examined patients [4].

One NPSLE syndrome, cognitive dysfunction, is observed to occur with a frequency of between 10.7% and 36% [3]. A recent review by Sciascia et al. reports that applying such tests as the Stanford-Binet Intelligence Test, the Wechsler Adult Intelligence Scale, the Complex Attention Task and the Pattern Comparison Task increases the detection rate of cognitive defects in patients with SLE, with values ranging from 21% to 80% [5]. In spite of this, some manifestations of cognitive dysfunction may still be misdiagnosed or underestimated and, consequently, not treated properly [6]. By utilizing 12 selected test scores of the ACR NPSLE battery and a cognitive impairment index, Kozora et al. [6] found that 23% of SLE patients without overt neuropsychiatric manifestation were cognitively impaired. Therefore, a clear need exists for the use of neuropsychiatric tests with adequate validity and reliability.

However, as not every test has its own language adaptation, physicians in other countries may encounter limitations in the evaluation of SLE patients when using them. To address this issue, the present study uses the Cambridge Neuropsychological Test Automated Battery (CANTAB). CANTAB was originally developed at the University of Cambridge in the 1980s but now is provided in a commercial capacity by Cambridge Cognition, which is a computer-based cognitive assessment system consisting of a battery of neuropsychological tests, administered to subjects using a touch screen computer. The use of CANTAB in clinical practice has several advantages. CANTAB employs non-verbal stimuli and requires non-verbal responses. This is of a partic-

ular relevance for patients with language impairment, but is also important for international studies. Secondly, as the program is designed to test different aspects of mental functioning, a performance profile may be chosen and constructed for a particular group of patients, for instance those with SLE. CANTAB tests are graded in difficulty and so can be used to assess a broad range of cognitive abilities. Recent studies show that the results of CANTAB subtests are modestly correlated with those of traditional subtests [7].

Aim

Therefore the aim of the study was to investigate the feasibility of the cognitive parameters of CANTAB in assessment in cognitive parameters in patients in relation to their autoantibody profile. To our knowledge, this is the first study using CANTAB to study cognitive impairment in patients with SLE. However, the key strengths of our study are firstly that the results are standardized and may be used in modeling and quantitative description of NPSLE, and secondly they are comparable and reproducible and, as such, may lead to meta-analyses of future studies conducted on larger populations of SLE patients from different centers.

Material and methods

Eligibility criteria

The study included a convenience sample of 32 patients with SLE (30 women and 2 men) aged 42.06 ±9.81 years. The diagnosis of SLE was based on the classification criteria for SLE updated in 1997 by the American College of Rheumatology [1]. The duration of SLE ranged from 2 to 24 years (mean 10.32 ±5.47 years). At the time of the study, none of the SLE patients were found to have disease activity as indicated by SELENA-SLEDAI > 6 or presented any overt neuropsychological signs or symptoms [8]. The mean duration of SLE was 9.96 ±5.69 years. The exclusion criteria for the SLE patients were a history of learning disabilities, a history of head injury, the presence of primary neurologic and psychiatric disorders, taking psychotropic or cognitive modifying medications, metabolic disturbances such as uremia and diabetes, and coexisting emotional distress. Pregnant women and people under 18 years were also excluded. The project was approved by the local Ethics Committee, No. RNN/123/13/KB. All participants gave their informed consent prior to the study.

Neuropsychological assessment

For neuropsychological assessment, the Cambridge Neuropsychological Test Automated Battery (Cambridge

Cognition, UK) was applied with license No. W/O7442; 1334087932. The following tests were used:

- Motor screening (MOT), which screens for visual, movement and comprehension difficulties. Results are expressed as the standard score of mean latency (MOT ML) and mean error (MOT ME).
- Big little circle (BLC), which estimates attention, comprehension and the ability to learn and follow simple rules, as well as rule reversals. Outcomes are expressed as the standard score of percentage correct actions.
- Paired associated learning (PAL), which assesses visual memory and new learning. Results are expressed as the standard score of total errors.
- Stockings of Cambridge (SOC), which screens spatial planning and motor control. Outcomes are expressed as the standard score of mean initial thinking time (SOC MITT), mean subsequent thinking time (SOC MSTT), and problems solved in minimum moves (SOC PSMM).
- The graded naming test (GNT), which screens lexical and semantic memory by assessing object-naming ability. Results are expressed as the standard score of percentage of correct answers.

The results of the aforementioned tests were referred automatically to determined ranges of norms matched according to age and gender, and standard scores were automatically provided by the CANTAB. Cognitive dysfunction was defined by results less than –0.5 of the standard score.

Laboratory investigations

For simultaneous autoantibody testing, blood was collected, and serum was centrifuged and stored at –70°C until assayed. However, only 26 patients agreed to blood collection. The Immuno Concepts Colorzyme ANA Test System (USA) was used to assess the ANA titer. The QUANTA Lite dsDNA ELISA kit (INOVA, USA) was used to detect anti-dsDNA antibodies, the Nucleosome IgG ELISA kit (D-tek, Belgium) was used to detect anti-nucleosome (aNuc), and INOVA QUANTA Lite Sm ELISA was used for anti-Sm antibodies. For assessment of anti-cardiolipin (aCL) antibodies, Autostat II ACA IgM and IgG kits (Hycor, USA) were applied.

Statistical analysis

Data estimation performed with the Shapiro-Wilk test did not confirm normal distribution of measured parameters. Therefore further statistical analyses with Spearman's rank correlation coefficient were used to estimate correlations, and Cochran's Q test was employed to estimate the reliability of the results. For detecting differences in cognitive outcomes across CANTAB tests, the Friedman test was employed. All analyses were performed with Statistica, version 10 (StatSoft, Poland). Resulting p values < 0.05 were considered to indicate significance. Despite the use of nonparametric tests, in order to present the results more clearly, the obtained results were presented as the mean and standard deviation, instead of the median and upper and lower quartiles.

Results

Clinical characteristics of studied patients according to classification by ACR criteria are shown in Table I.

Results of CANTAB tests obtained by patients with SLE and expressed as standard scores are shown in Table II.

In patients with SLE, standard scores were found lower than those of norms matched according to age and gender in the following tests: the graded naming test (GNT: –0.8 ±0.8), problems solved in minimum moves of stockings of Cambridge (SOC PSMM: –0.4 ±0.9), paired associated learning (PAL: –1.88 ±3.58) and big little circle (BLC: –0.3 ±1.9).

The frequencies of cognitive deficits in SLE revealed by CANTAB and assessed with the Cochran Q test are shown in Figure 1.

The results of the Friedman test demonstrated that among the cognitive outcomes obtained in CANTAB tests, those derived from PAL (–1.88 ±3.58) were found to be the most impaired ($p < 0.001$) (Fig. 2).

Table I. Clinical characteristic of SLE patients according to classification ACR criteria

Manifestation	Number	%
Malar rash	17/32	53.1
DLE	6/32	18.7
Oral ulcers	5/32	15.6
Photosensitivity	20/32	62.5
Arthritis	31/32	96.8
Serositis	2/32	6.2
Renal disorder	4/32	12.5
NPSLE in previous medical records only	3/32	9.3
Hematological disorder	26/32	81.2
Anti-dsDNA	4/32	12.5
Anti-Sm	5/32	15.6
Anti-CL	15/32	46.8
ANA positive	32/32	100

Table II. Results of standard scores of CANTAB tests obtained by patients with SLE

CANTAB test	No patients included	Mean	Median	Min	Max	Lower quartile	Upper quartile	SD
MOT ML (mean latency of motor screening)	32	0.9	1.0	−0.3	1.7	0.8	1.3	0.5
MOT ME (mean error of motor screening)	32	0.4	0.4	−0.3	1.6	0.2	0.4	0.3
BLC (big/little circle)	32	−0.3	0.1	−8.6	0.1	0.1	0.1	1.9
PAL (paired associates learning)	32	−1.8	−0.8	−12.6	6.4	−2.3	−0.1	3.5
SOC MITT (mean initial thinking time)	31*	0.9	0.9	0.2	1.4	0.8	1.1	0.3
SOC MSTT (mean subsequent thinking time of stockings of Cambridge)	31*	0.4	0.6	−2.7	1.2	0.0	1.0	0.8
SOC PSMM (problems solved in minimum moves)	32	−0.4	−0.5	−2.1	1.1	−1.3	0.5	0.9
GNT (graded naming test)	32	−0.8	−0.8	−2.7	0.6	−1.4	−0.2	0.8

One female patient did not complete the test

GNT scores under −0.5 were found in approximately two thirds of the SLE patients. The results of the PAL test, and mean subsequent thinking time in stockings of Cambridge (SOC) were found to be lower than −0.5 in approximately half of the patients.

Results of correlations between CANTAB tests and the autoantibody profile in SLE are shown in Table III.

Mean error of motor screening (MOT ME) negatively correlated with mean latency of motor screening (MOT ML) ($r = -0.55$). The PAL values significantly correlated with SOC mean subsequent thinking time (SOC MSTT) scores ($r = 0.38$) and with GNT scores ($r = 0.36$). The presence of anti-dsDNA antibody correlated negatively with MOT ME values ($r = -0.46$). Anti-Nuc antibodies correlated with MOT ML values ($r = 0.41$) and negatively correlated with MOT ME ($r = -0.58$). The levels of anti-Sm, anti-CL IgM and IgG did not correlate significantly with the outcomes of CANTAB. The age of patients
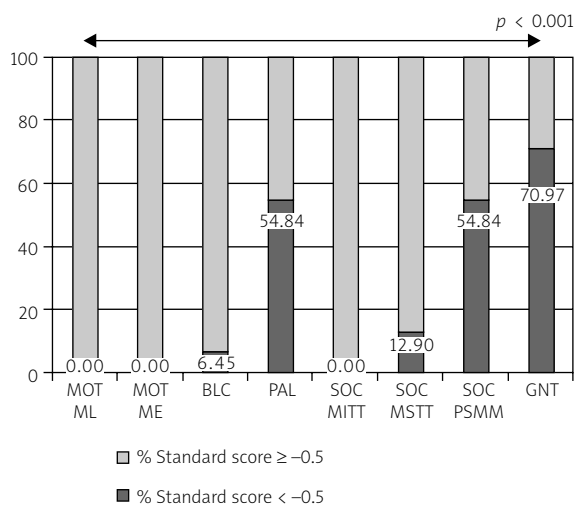

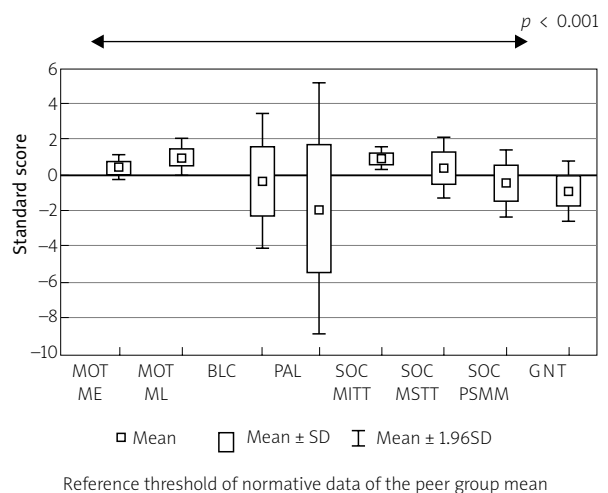**Fig. 1.** Frequency of cognitive dysfunctions in SLE revealed in CANTAB tests

Reference threshold of normative data of the peer group mean

Fig. 2. Comparison of cognitive dysfunctions in results of standard scores of CANTAB tests in SLE patients

Table III. Results of correlations between CANTAB tests and autoantibodies profile in SLE

	MOT ML	MOT ME	BLC	PAL	SOC MITT	SOC MSTT	SOC PSMM	GNT	Anti-DNA	Anti-Sm	Anti-Nuc	Anti-CL IgM	Anti-ACL IgG	Age	SLE duration
MOT ML	–	–0.55*	0.11	0.05	0.13	–0.12	–0.24	–0.04	0.25	0.12	0.41*	0.09	–0.01	0.30	–0.29
MOT ME	–0.55*	–	0.26	0.00	0.21	0.29	0.24	0.04	–0.46*	–0.10	–0.58*	–0.30	–0.10	–0.36*	0.01
BLC	0.11	0.26	–	–0.07	0.24	–0.09	–0.03	–0.05	–0.06	–0.05	–0.06	–0.04	0.14	0.53*	0.23
PAL	0.05	0.00	–0.07	–	–0.22	0.38*	0.07	0.36*	–0.18	–0.01	–0.10	–0.11	–0.08	–0.31	–0.09
SOC MITT	0.13	0.21	0.24	–0.22	–	0.07	–0.19	0.12	–0.26	0.09	–0.07	0.17	0.39	–0.01	–0.20
SOC MSTT	–0.12	0.29	–0.09	0.38*	0.07	–	0.28	–0.05	0.06	0.09	–0.16	–0.03	–0.03	–0.43*	0.01
SOC PSMM	–0.24	0.24	–0.03	0.07	–0.19	0.28	–	0.06	–0.16	–0.30	–0.18	0.16	0.17	–0.15	0.05
GNT	–0.04	0.04	–0.05	0.36*	0.12	–0.05	0.06	–	–0.23	–0.04	–0.31	–0.18	0.04	0.15	–0.16
Anti-dsDNA	0.25	–0.46*	–0.06	–0.18	–0.26	0.06	–0.16	–0.23	–	–0.11	0.62*	0.01	–0.25	0.07	0.14
Anti-Sm	0.12	–0.10	–0.05	–0.01	0.09	0.09	–0.30	–0.04	–0.11	–	0.02	0.39*	0.36	0.18	–0.26
Anti-Nuc	0.41*	–0.58*	–0.06	–0.10	–0.07	–0.16	–0.18	–0.31	0.62*	0.02	–	0.12	–0.01	0.09	0.10
Anti-CL IgM	0.09	–0.30	–0.04	–0.11	0.17	–0.03	0.16	–0.18	0.01	0.39*	0.12	–	0.87*	0.17	0.08
Anti-CL IgG	–0.01	–0.10	0.14	–0.08	0.39	–0.03	0.17	0.04	–0.25	0.36	–0.01	0.87*	–	0.25	0.08
Age	0.30	–0.36*	0.53*	–0.31	–0.01	–0.43*	–0.15	0.15	0.07	0.18	0.09	0.17	0.25	–	0.40*
SLE duration	–0.29	0.01	0.23	–0.09	–0.20	0.01	0.05	–0.16	0.14	–0.26	0.10	0.08	0.08	0.40*	–

*$p < 0.05$

negatively correlated with MOT ME ($r = -0.36$), positively with BLC ($r = 0.53$), and negatively with SOC MSTT ($r = -0.43$). The level of anti-Nuc antibodies correlated with anti-dsDNA level ($r = 0.62$), while anti-CL IgM level correlated with levels of anti-Sm ($r = 0.39$) and anti-CL IgG ($r = 0.87$).

Discussion

In our study the most frequent abnormalities were found to be those related to lexical and semantic memory, revealed by the GNT to be present in more than two thirds of SLE patients. Semantic memory is a distinct part of the declarative memory system, comprising knowledge of facts, vocabulary, and concepts acquired in time, through everyday life [9]. The impairment of such cognitive functions as lexical and semantic memory may be manifested in daily life by difficulties in activities related to word finding and picture naming. Moreover, spatial planning and spatial working memory, assessed by the SOC, together with visual memory and new learning, assessed with the PAL test, were also found to be depressed.

Cognitive impairment or cognitive deficit is an inclusive term to describe any characteristic that acts as a barrier to the cognition process. Thus the term may describe deficits in global intellectual performance, such as mental retardation, or it may describe specific deficits in cognitive abilities (learning disorders, dyslexia) [10].

Spatial working memory reflects one's ability to temporarily store and process information regarding the surrounding environment [11]. This temporary store enables complex tasks to be performed while keeping information in mind [11]. The visuospatial component of working memory is assumed to hold information about what can be seen. Besides temporary storage, it plays a role in the manipulation of spatial and visual information, such as remembering shapes and colors, determining the location of objects in space, or assessing their speed. Spatial working memory is also engaged in tasks which involve the planning of spatial movements, such as a route through a complex building. It is principally represented within the right hemisphere of the brain [12].

Spatial working memory, assessed with PAL, turned out to be affected to the highest degree in the SLE patients evaluated in the present study. PAL and GNT when combined were found to be highly accurate in detecting the cognitive dysfunction characteristic of preclinical Alzheimer's disease [13]. Blackwell et al. [13] demonstrated that these tests allow a highly accurate assessment to be made of the level of risk for an individual with mild memory impairment to develop Alzheimer's disease. Despite the absence of a comparative study of cognitive functions in SLE assessed by CANTAB, several lines of evidence indicate the clinical relevance of the presence of brain abnormalities in SLE patients which lack overt neuropsychiatric manifestation [6]. Kozora et al. [6] found that the results of neuropsychiatric evaluation obtained by the Digit Symbol, Letter-Number Sequencing Test, California Verbal Learning and Digit Vigilance Test were significantly lower than those of the control group [6]. In contrast, Monastero et al. [14] reported no significant differences in WAIS-Digit Span, Rey's Word-List learning IR, Rey's Word-List Learning DR, Rey's Complex Figure Copy, Rey's Figure Recall, Phonemic Fluency, or Trail Making B between non-NPSLE and NPSLE groups. Moreover, non-NPSLE patients did not differ significantly in cognitive functions from those of mixed connective tissue disease, which suggests that in autoimmune connective tissue diseases, the involvement of the nervous system can be a crucial factor in terms of cognitive dysfunction [15]. In a recent imaging study conducted on thirteen female patients with SLE, but without overt NPSLE, functional magnetic resonance indicated that learning and memory-related brain activity dynamics were found to be altered [16]. Patients with SLE demonstrated significantly less deactivation in the default mode network and greater activation in the task-positive network, reflecting greater recruitment of both networks. In conclusion, increased brain activation in patients with SLE during learning is suggested to reflect compensatory mechanisms to overcome memory impairment [16].

The SOC outcomes obtained in our study show a decrease in spatial planning and spatial working in SLE patients. This test gives a measure of frontal lobe function. Since declines in visual memory and new learning, assessed by PAL, were found to be the most significant tested features in SLE patients, and considering that PAL is sensitive to changes in medial temporal lobe functioning, the CANTAB test appears to be a non-invasive and easily conducted procedure which can potentially be used in assessing the probable localization of the affected area within the brain of an SLE patient.

Our results regarding the extent and pattern of cognitive function in SLE patients in remission appear to be in accordance with the clinical picture of cases with cognitive decline developing in a subclinical course but appear to lack any overt clinical neuropsychiatric manifestation. Due to the sparse nature of established therapies and rehabilitation programs regarding cognitive functions in SLE, and considering their clinical importance in the daily life of patients, there is a need for better diagnoses of cognitive dysfunction to be performed in accordance with international reference standards. These should be included in the management protocols

for SLE patients and lead to the introduction of cognitive rehabilitation programs.

Unfortunately, the pathogenesis of cognitive dysfunction in SLE is not fully understood. Currently, it is attributed to an obscure combination of several variables, such as production of autoantibodies, immune complex deposition, cytotoxic damage of neurons, expression of inflammatory mediators, recruitment of inflammatory cells, and thrombosis [17, 18]. Mikdashi and Handerwerger report that the presence of antiphospholipid and anti-Ro/SSA antibodies are independent predictors of significant neuropsychiatric damage [19]. In contrast, in our study the levels of anti-CL IgM and IgG did not correlate significantly with the outcomes of CANTAB. However, anti-dsDNA antibody presence correlated negatively with MOT ME, while anti-Nuc antibodies correlated positively with MOT ML, and correlated negatively with MOT ME. However, our study was conducted on a limited number of patients. Up to now, among antinuclear antibodies, only anti-dsDNA has been found to be capable of cross-reacting with the NMDA glutamate receptor and producing neuronal injury and death [20]. Some studies have confirmed the role of anti-P antibodies in psychiatric manifestations of NPSLE, although this is disputed by others [21]. Anti-nucleosome antibodies are considered as highly sensitive and specific for the diagnosis of SLE, especially when the anti-dsDNA antibodies are absent [22]. They could serve as additional disease activity markers in the assessment of SLE disease activity, but there is a lack of evidence of their role in cognitive decline at the molecular level.

One needs to remember that also risk factors for atherosclerosis and subsequent cardiovascular disease (CVD) in SLE are contributory to cognitive decline [23]. Traditional CVD risk factors include age, hypertension, diabetes mellitus, dyslipidemia, previous cerebrovascular accidents or ischemic heart disease, menopause and smoking, whereas lupus nephritis, pro-inflammatory cytokines, inflammatory mediators, antiphospholipid antibodies, anti-oxLDL antibodies and corticosteroids are lupus specific [21]. Evidence supports the potential utility of assessment of ejection fraction and blood pressure to determine a phenotypic profile associated with increased risk of cognitive impairment [24]. Therefore, the mechanisms forming the basis of cognitive dysfunction in SLE can be attributed not only to direct neurotoxic effects, vasculopathy and in some cases to a prothrombotic state, but also to hypercholesterolemia and accelerated atherosclerosis, which is diagnosed in SLE more and more often.

Several limitations of our study must be emphasized. Firstly, it was an observational study limited to a convenience sample of 32 SLE patients, and only 26 of them gave permission for blood collection. Secondly, only patients without overt neuropsychiatric manifestation were included in the study. It would have been of great interest to compare the CANTAB outcomes with those obtained in NPSLE patients, and further to evaluate the results in patients with other autoimmune connective tissue disorders, especially antiphospholipid syndrome; however, this will have to await future studies. Thirdly, the observation period of the study was short, and further longitudinal studies with repetitive measurement are needed to provide more detailed and precise descriptions of both the pattern and dynamics of cognitive impairment in the course of SLE.

The key strength of our study is that it employs a battery of tests with non-verbal stimuli and non-verbal responses in the assessment of cognitive functions. In addition, the results are expressed as a standard score, thus making it more comparable and reproducible in future studies conducted on larger populations from different centers. This reproducibility may prove valuable in future meta-analyses and allow future conclusions to be drawn from a more comprehensive evidence base. Therefore, further studies addressing the aforementioned values as contributory variables in cognitive impairment and its pattern in SLE patients are required.

References

1. ACR Ad Hoc Committee of Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999; 42: 599-608

2. Hochberg M. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40: 1725-1734.

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

4. Hawro T, Bogucki A, Sysa-Jędrzejowska A, et al. Neurological disorders in systemic lupus erythematosus patients. Pol Merkur Lek 2009; 26: 43-48.

5. Sciascia S, Bertolaccini M, Baldovino S, et al. Central nervous system involvement in systemic lupus erythematosus: Overview on classification criteria. Autoimmun Rev 2013; 12: 426-429.

6. Kozora E, Filley C, Zhang L, et al. Immune function and brain abnormalities in patients with systemic lupus erythematosus without overt neuropsychiatric manifestations. Lupus 2012; 21: 402-411.

7. Smith P, Need A, Cirulli E, et al. A comparison of the Cambridge Automated Neuropsychological Test Battery (CANTAB) with

"traditional" neuropsychological testing instruments. J Clin Exp Neuropsychol 2013; 35: 319-328.

8. Lam G, Petri M. Assessment of systemic lupus erythematosus. Clin Exp Rheumatol 2005; 23 (5 Suppl 39): 120-132.

9. Coren S, Ward LM, Enns JT. Sensation and Perception. Harcourt Brace 1999; 9.

10. Baddeley A, Kopelman M, Wilson B. The Psychology of Memory. In: The Essential Handbook of Memory Disorders for Clinicians. Baddeley AD, Kopelman MD, Wilson BA (eds.). John Wiley & Sons, Chichester 2004; 1-15.

11. Ang S, Lee K. Central executive involvement in children's spatial memory. Memory 2008; 16: 918-933.

12. Baddeley A. The episodic buffer: a new component of memory? Trends Cogn Sci 2000; 4: 417-423.

13. Blackwell A, Sahakian B, Vesey R, et al. Detecting dementia: novel neuropsychological markers of preclinical Alzheimer's disease. Dement Geriatr Cogn Dis 2004; 17: 42-48.

14. Monastero R, Bettini P, Del Zotto E, et al. Prevalence and pattern of cognitive impairment in systemic lupus erythematosus patients with and without overt neuropsychiatric manifestations. J Neurol Sci 2001; 84: 33-39.

15. Nowicka-Sauer K, Czuszynska Z, Majkowicz M, et al. Neuropsychological assessment in mixed connective tissue disease: comparison with systemic lupus erythematosus. Lupus 2012; 21: 927-933.

16. Shapira-Lichter I, Vakil E, Litinsky I, et al. Learning and memory-related brain activity dynamics are altered in systemic lupus erythematosus: a functional magnetic resonance imaging study. Lupus 2013; 22: 562-573.

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

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

19. Mikdashi J, Handwerger B. Predictors of neuropsychiatric damage in systemic lupus erythematosus: data from the Maryland lupus cohort. Rheumatology 2004; 43: 1555-1560.

20. Kotzin BL, Kozora E. Anti-DNA meets NMDA in neuropsychiatric lupus. Nat Med 2001; 7: 1175-1176.

21. Eber T, Chapman J, Shoenfeld Y. Anti-ribosomal P-protein and its role in psychiatric manifestations of systemic lupus erythematosus: myth or reality? Lupus 2005; 14: 571-575.

22. Suleiman S, Kamaliah D, Nadeem A, et al. Anti-nucleosome antibodies as a disease activity marker in patients with systemic lupus erythematosus. Int J Rheum Dis 2009; 12: 100-106.

23. Sinicato NA, da Silva Cardoso PA, Appenzeller S. Risk factors in cardiovascular disease in systemic lupus erythematosus. Curr Cardiol Rev 2013; 9: 15-19.

24. Jurgens CY, Faulkner KM, Lee CS. Phenotypic profiling of cognitive impairment risk among patients with heart failure: a literature review of the usefulness of cardiac-related variables. Eur J Cardiovasc Nurs 2013; 12: 109-131.