Cognitive impairment, event-related potentials and immunological status in patients with systemic lupus erythematosus

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Conflict of interest

None declared

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Abstract

Background. Cognitive impairment (CI) is a frequent problem in lupus patients, regardless of their overt neuropsychiatric (NP) involvement.

Objectives. The aim of our study was to test cognitive abilities in systemic lupus erythematosus (SLE) patients using neuropsychological testing and event-related potentials (ERPs), and to search for their cognitive abilities correlations with a wide range of auto-antibodies.

Material and methods. A total of 37 SLE patients were subjected to a battery of neuropsychological tests, recommended by the American College of Rheumatology (ACR), and to ERPs. They were also tested for a wide range of auto-antibodies (anti-cardiolipin (aCL), anti-β₂-glycoprotein I (anti-β₂-GPI), lupus anticoagulant, anti-dsDNA, anti-nucleosome, anti-ribosomal P (anti-Rib-P), anti-ganglioside, anti-Ro/SS-A, and anti-La/SS-B).

Results. Cognitive impairment was found in 35% of patients, mostly with NP SLE (NPSLE), and was associated with higher disease activity, measured by the SLE Disease Activity Index (SLEDAI), and with a longer duration of central nervous system (CNS) involvement. There were no differences in the immunological status between CI patients and those without cognitive decline, but some antibodies were correlated with worse results in certain neuropsychological tests (anti-dsDNA and worse results of Rey Complex Figure Test – RCFTc for copying and RCFTr for recall, and of verbal fluency test (VFT); aCL IgG and worse results in Digit Span (DS) and in RCFTc). Event-related potentials showed prolonged N200 and P300 latencies in SLE patients in comparison to controls, but no differences were found between SLE and NPSLE patients. Mean P300 latency was significantly longer in patients without anti-nucleosome antibodies.

Conclusions. Event-related potentials can be used as a complementary tool in assessing CI in SLE patients. The immunological status of patients with CI did not differ from that of patients without cognitive problems.

Key words: systemic lupus erythematosus, cognitive impairment, auto-antibodies, event-related potentials

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a heterogeneous clinical picture. Nervous system involvement is frequently observed, affecting 14–75% of patients. In 1999, the American College of Rheumatology (ACR) proposed the nomenclature and definitions of 19 neuropsychiatric (NP) syndromes in SLE.¹ One of the most frequent neurological problems is cognitive impairment (CI).

Cognitive impairment may concern a various extent of particular domains, such as memory, executive function, visuospatial abilities, and others. It is characterized by a fluctuating course and may be affected by other factors (especially depression, fatigue and pain). Cognitive impairment has been observed both in patients with previous NP involvement in the course of neuropsychiatric SLE (NPSLE) and in patients without overt central nervous system (CNS) disease.

Over the past decade, there has been growing interest in cognitive dysfunction in SLE patients. Since 1999, ACR has recommended a battery of neuropsychological tests, validated by Kozora et al. in 2004 and dedicated to this particular group of patients, covering the cognitive domains most frequently affected in the course of SLE.^{1,2} Apart from neuropsychological measures, event-related potentials (ERPs) are also considered a useful tool in an objective assessment of cognitive abilities. However, ERPs parameters as an electrophysiological index of cognitive function have rarely been investigated in SLE patients.^{3–6}

The relationship between different auto-antibodies and NP syndromes in SLE remains a matter under investigation. Some auto-antibodies, such as antiphospholipid, are widely associated with nervous system involvement, while others (e.g., anti-Rib-P and anti-gangliosides) have been the subject of only a few studies and with equivocal results.

The purpose of our study was to use neuropsychological testing and ERPs in order to evaluate cognitive functions in SLE patients regarding their NPSLE status. We also aimed to analyze the relationships between cognitive performance and SLE clinical activity, as well as the immunological status of patients, including a wide range of auto-antibodies.

Material and methods

Patients

Thirty-seven patients (all Caucasian, 35 females, 2 males, aged 18–60 years, mean age: 38.3 years) were enrolled in the study (Table 1). All the patients fulfilled the 1997 updated ACR criteria for the diagnosis of SLE.^{7,8} Patients were recruited from the Department of Rheumatology and Internal Diseases of Wrocław Medical University, Poland. Subjects with a known history of comorbid neurological

Table 1. Demographic and clinical characteristics of patients with systemic lupus erythematosus (SLE)

Characteristic	Patients (n = 37)
Age [years]	18–60 (mean 38.3)
Gender	35 females, 2 males
Disease duration [years]	3–31 (mean 10)
NPSLE	24
Non-NPSLE	13
Mean NPSLE duration [years]	6
SLEDAI score	0–16 (mean 9.59)
Active NPSLE	14

NPSLE – neuropsychiatric systemic lupus erythematosus; SLEDAI – systemic lupus erythematosus Disease Activity Index.

or psychiatric disorders not associated with SLE, with a history of substance abuse or with learning disability were excluded from the study. The control group consisted of 30 healthy volunteers, matched for age, gender and education level with the SLE patients.

The study was approved by the Bioethics Committee of Wrocław Medical University (No. KB-117/2008) and carried out in accordance with the Helsinki protocol. Patients were enrolled after they had provided informed written consent.

Clinical assessment

Clinical assessment included the history based on medical records and physical examination. The following data was collected: disease duration, duration of CNS involvement and disease activity measured with the SLE Disease Activity Index (SLEDAI). In SLE patients, NP involvement was diagnosed in accordance with ACR nomenclature and case definitions.¹ Information on current and past medication was obtained.

Neuropsychological tests

To evaluate the patients' cognitive performance, the following neuropsychological tests were carried out: Auditory Verbal Learning Test (AVLT) – assessing short-term memory and the ability to learn new verbal material; Trail Making Test (TMT) – a measure of psychomotor speed, visuospatial operating memory and attention shifting; Rey Complex Figure Test (copying – RCFTc; recall – RCFTr) – evaluating visuospatial abilities, memory, attention, planning, working non-verbal memory, and executive functions; Digit Span (DS) from the Wechsler Adult Intelligence Scale (WAIS-R) – testing direct auditory memory and operating memory; Verbal Fluency Test (VFT; generating lists of words starting with K and belonging to the category “animals”) – assessing categorization abilities and executive functions; and Stroop Test (ST) – as a measure of attention concentration and divisibility. From the battery recommended by ACR, we chose tests available in Polish

versions with adequate normative data. The Beck Depression Inventory (BDI) was applied to estimate the levels of depression. All the tests were explained to the subjects, administered and evaluated by a neuropsychologist, and the results were referred to normative age-adjusted values.

The tests were classified according to the assessed cognitive domains: AVLT, DS and RCFT_r as a measure of memory; TMT, VFT, ST – as a measure of attention and executive functions; and RCFT_c – as a measure of visuospatial skills. Those subjects who scored worse than the normative values in the tests representing at least 2 of these 3 cognitive domains were assigned as cognitively impaired. In addition, z-scores were calculated for the results of particular tests and they were averaged for the tests representing particular cognitive domains.

Event-related potentials

Auditory ERPs were elicited using the “oddball paradigm”, with target stimuli randomly interspersed among non-target ones. Auditory stimuli were tones of 70 dB intensity and 200 ms duration. The target tones (high frequency: 2 kHz) accounted for 20% of the time of each trial and the non-target tones (low frequency: 1 kHz) for 80% of the time. The subjects lay awake in a semi-darkened room and were asked to count the target stimuli quietly in their heads. Event-related potentials were recorded in Fz, Cz and Pz (points on the skull surface according to the International 10–20 system of EEG/SEP recording) according to the 10–20 system, with reference to linked earlobes and with a forearm ground. Ag/AgCl surface electrodes were used and their impedance was maintained below 5 k Ω . The responses were analyzed with a Nicolet 1000 Viking (Natus Medical Inc., Pleasanton, USA), with a 0.30/s, 70 Hz bandpass filter, a sweep time of 1000 ms and a pre-stimulus baseline of 250 ms. At least 30 target trials were averaged in each run. Two runs were performed for every subject. P300 was identified as the positive component with a latency of 300–500 ms and N200 as the negative component with a latency of 180–300 ms after the start of the stimulus. The latencies and amplitudes (“peak to baseline”) of P300 and N200 were determined.

The neuropsychological tests and ERPs in the patients were performed on the same day, in morning hours.

Antibodies

The auto-antibodies tested in patient sera included: antinuclear antibodies, anti-dsDNA antibodies, anti-nucleosome antibodies, anti-cardiolipin antibodies (aCL) IgG and IgM isotypes, anti- β 2-glycoprotein I antibodies (anti- β 2-GPI) IgM and IgG isotypes, anti- β 2-GPI/oxLDL IgG and IgM antibodies, anti-ribosomal P antibodies (anti-Rib-P), anti-ganglioside antibodies, anti-Ro/SS-A, anti-La/SS-B, and lupus anticoagulant. We also evaluated the level of the following cytokines: interleukin (IL)-6, IL-10 (R&D

Systems, Minneapolis, USA) and IL-17 (Diacclone SAS, Besançon, France). Anti-dsDNA, anti-nucleosome antibodies, aCL, anti- β 2-GPI, and anti-Rib-P antibodies were tested with the enzyme-linked immunosorbent assay (ELISA) method (EUROIMMUN, Lübeck, Germany), anti-ganglioside with a dot blot test (EUROIMMUN), anti-Ro/SS-A and anti-La/SS-B with the ELISA method by Inova Health System (Falls Church, USA). All the tests were performed according to the manufacturers’ recommendations. The lupus anticoagulant levels were measured with activated thromboplastin time, kaolin clotting time and diluted Russel viper venom time.

Statistical analysis

The subgroup of CI patients was compared with those without CI with regard to disease-related variables (duration of SLE, duration of CNS involvement, NPSLE criteria, SLEDAI score, dose of corticosteroids used) and all the studied immunological parameters. Potential relationships were also investigated between z-scores (for particular tests and cognitive domains), disease-related variables and immunological parameters.

The level of depression was referred to cognitive performance and immunological parameters.

The ERPs parameters in the SLE patients were analyzed in comparison to the controls. They were referred to disease-related variables and immunological parameters.

Parameters in groups were expressed as median and quartiles or as mean, median, quartiles, and standard deviation (SD). The statistical significance between means for different groups was calculated with the one-way analysis of variance (ANOVA), or alternatively by using the non-parametric Kruskal-Wallis test, when the variances in groups were not homogeneous (the homogeneity of variance was determined with Bartlett’s test) or when the number of cases was too small. The statistical significance between frequencies was calculated with the χ^2 test with Yates’s correction or, if the expected value was <5, with the Fisher’s exact test.

Relationships between 2 parameters were assessed using a correlation analysis and Pearson’s correlation coefficients were calculated.

A p-value <0.05 was required to reject the null hypothesis. Statistical analysis was performed using the EPIINFO v. 3.5.2 (December 17, 2010) software package (CDC, Atlanta, USA).

Results

In SLE patients, the disease duration was 3–31 years (mean: 10 years). The SLEDAI score ranged from 0 to 16 (mean: 9.59). There were 24 patients with NP involvement and 13 non-NPSLE patients. The mean duration of NP involvement was 6 years. Active NP symptoms were

diagnosed in 14 patients. The most common NP manifestations were mood disorders – mainly depression – in 18 patients; cerebrovascular disease (stroke or transient ischemic attack – TIA, or cerebral sinus thrombosis) was recognized in 7 patients, seizures in 4 patients, psychosis in 4 patients, polyneuropathy in 3 patients, cranial neuropathy in 2 patients, acute confusional state in 2 patients, and severe headache in 1 patient. More than 1 NP manifestation was diagnosed in 12 patients. All the patients were treated with corticosteroids; the mean dose used was 15 mg/day of prednisone.

Antibodies

Auto-antibodies and the cytokine status were evaluated in all the patients. Elevated levels of IL-6 were detected in 4 patients (10.8%), of IL-10 in 14 patients (37.8%) and of IL-17 in 10 patients (27%).

Anti-dsDNA antibodies were detected in 14 patients (38%), anti-Rib-P antibodies in 4 patients (11%) and anti-nucleosome antibodies in 18 patients (49%). Anti-phospholipid (APL) antibodies in medium and high titers were as follows: aCL IgG were detected in 15 patients (40.5%), aCL IgM in 10 (27%), anti- β 2-GPI IgG in 4 (11%), and anti- β 2-GPI IgM in 10 (27%). Lupus anticoagulant was detected in 9 patients (24%). Anti-ganglioside antibodies were detected in 12 patients (32%), anti-Ro/SSA antibodies in 16 patients (43%) and anti-La/SSB antibodies in 10 patients (27%).

Neuropsychological tests – cognitive impairment

In SLE patients, 21 subjects had abnormal scores in AVLT (25 in the delayed part of AVLT), 22 in TMT, 14 in DS, 7 in RCFTc, 13 in RCFTTr, 25 in VFTI (VFT-letter), 14 in VFTs (VFT-semantic), and 4 in ST.

Fifteen patients showed impaired performance in at least 2 tests evaluating memory (AVLT, DS, RCFTTr), 19 in the field of attention and executive functions (TMT, VF, ST) and 4 presented with impaired visuo-spatial skills (RCFTc). Overall, 13 subjects (35%) who showed deficits in at least 2 of these cognitive domains were assigned to the cognitively impaired (CI) subgroup. The CI subgroup, in comparison to the remaining patients, showed significantly higher SLEDAI scores (12.7 ± 6.44 vs 7.8 ± 4.4 , respectively; $p = 0.01$). Among CI patients, 10 subjects fulfilled the criteria for NPSLE and 3 did not. Neuropsychiatric SLE patients with CI had a significantly longer duration of CNS involvement than those without CI (8 ± 5 years vs 4 ± 2 years, respectively; $p = 0.01$). There were no significant differences between patients with or without CI in terms of the duration of the disease, dose of corticosteroids, BDI score, or diagnosed depression.

Analyzing the relationships between z-scores for the neuropsychological tests and disease-related variables, we found a significant correlation between the z-score for the delayed part of AVLT and the SLEDAI results ($R = 0.42$, $p = 0.006$). No other significant relationships were found.

The subgroups with and without CI did not differ in the presence of particular auto-antibodies/cytokines. Several significant correlations were found between immunological markers and z-scores for particular neuropsychological tests. Patients with higher levels of IL-17 had higher z-scores (and worse results) for DS and RCFTc. Those with detectable anti-dsDNA antibodies had higher z-scores (and worse results) for RCFTc, RCFTTr and VFT. The patients positive for anti- β 2-GPI/oxLDL IgM antibodies showed lower z-scores (and worse results) for TMT. Those positive for aCL IgG antibodies had higher z-scores (and worse results) for DS and RCFTc (Table 2).

Table 2. Comparison of z-scores for neuropsychological tests between the subgroups of SLE patients with positive (+) or negative (–) immunological parameters

Parameters	DS z-score median (quartiles)	RCFTc z-score median (quartiles)	RCFTTr z-score median (quartiles)	TMT z-score median (quartiles)	VFT z-score median (quartiles)
IL-17 (+)	1.132 (0.698–1.363)	0.522 (0.489–0.522)	1.261 (0.478–1.390)	0.485 (0.225–0.840)	0.748 (0.683–0.896)
IL-17 (–)	0.665 (0.300–0.965)	0.185 (0.185–0.522)	0.603 (0.245–1.089)	0.799 (0.544–1.017)	0.534 (0.255–1.323)
p-value*	0.044	0.026	0.070	0.068	0.720
Anti-dsDNA (+)	0.965 (0.633–1.363)	0.522 (0.489–0.522)	1.321 (0.727–1.450)	0.691 (0.383–0.856)	0.896 (0.683–1.323)
Anti-dsDNA (–)	0.698 (0.300–1.030)	0.185 (0.185–0.522)	0.478 (0.245–1.020)	0.441 (0.256–0.835)	0.469 (0.255–0.896)
p-value*	0.260	0.017	0.003	0.230	0.021
oxLDL/ β 2 IgM (+)	0.965 (0.365–1.298)	0.185 (0.185–0.522)	0.486 (0.245–1.321)	0.370 (0.218–0.630)	0.427 (0.255–0.683)
oxLDL/ β 2 IgM (–)	0.698 (0.365–1.030)	0.522 (0.185–0.522)	0.603 (0.366–1.201)	0.609 (0.317–0.918)	0.896 (0.386–1.323)
p-value*	0.520	0.180	0.660	0.049	0.090
aCL IgG (+)	1.298 (0.633–1.363)	0.522 (0.185–0.522)	1.201 (0.478–1.390)	0.671 (0.256–0.856)	0.683 (0.469–1.323)
aCL IgG (–)	0.698 (0.300–0.965)	0.489 (0.185–0.522)	0.478 (0.306–1.080)	0.441 (0.297–0.835)	0.683 (0.255–1.026)
p-value*	0.038	0.250	0.030	0.720	0.310

SLE – systemic lupus erythematosus; IL-17 – interleukin-17; DS – Digit Span; RCFTc – Rey Complex Figure Test (copying); RCFTTr – Rey Complex Figure Test (recall); TMT – Trail Making Test; VFT – Verbal Fluency Test; * Kruskal-Wallis test; p-values in bold are statistically significant.

Event-related potentials

The mean values for N200 and P300 latencies were significantly greater in SLE patients than in controls (Table 3). No significant differences were found for P300 amplitude, but there was a trend toward a higher N200 amplitude in SLE patients in comparison to controls. Abnormalities were found in 35% of SLE patients in terms of N200 (prolonged latency) and in 62.5% in terms of P300 (lack of the P300 component in 1 subject, prolonged latency and/or lowered amplitude in 24).

Within the NPSLE subgroup, abnormalities were found in 56% of N200 and in 68.7% of P300, while 18.7% had no

ERPs abnormalities. Within the non-NPSLE subgroup, 28.6% presented with abnormal N200 and 62% with abnormal P300 parameters, while 33% had no ERPs abnormalities. The mean values of both N200 and P300 parameters did not differ significantly between the NPSLE and non-NPSLE subgroups, even after controlling for depression (Table 3).

There was a trend (but not significant, $p = 0.06$) toward longer N200 latency in the subgroup of patients with less active disease (SLEDAI <6), but no other relationships were found between the SLEDAI scores and ERPs parameters.

Mean P300 latency was significantly longer in the subgroup of patients with an absence of anti-nucleosome

Table 3. Comparison of the N200 and P300 parameters between patients with SLE and controls (A), NPSLE and non-NPSLE and patients with SLEDAI >6 and <6 (B)

Parameters	Controls mean median (quartiles) SD	SLE patients mean median (quartiles) SD	p-value
N200 Fz lat	209.6 205.0 (197.0–220.0) 22.1	224.8 223.0 (205.0–238.0) 30.1	0.0177*
N200 Fz ampl	4.25 3.60 (1.90–5.80) 2.97	5.86 5.20 (1.40–8.40) 4.41	0.203**
N200 Cz lat	208.0 204.0 (196.0–217.0) 21.5	223.1 221.0 (202.0–237.0) 31.0	0.0193*
N200 Cz ampl	3.38 2.10 (1.20–4.40) 2.98	5.17 3.90 (2.30–7.90) 3.66	0.0235**
N200 Pz lat	209.0 205.0 (19.0–219.0) 21.1	223.9 220.0 (204.0–235.0) 31.4	0.0216*
N200 Pz ampl	2.38 1.80 (1.00–3.00) 2.20	4.16 3.50 (1.60–6.10) 3.19	0.0073**
P300 Fz lat	320.6 323.0 (310.0–335.0) 22.5	347.8 349.5 (333.0–366.5) 31.1	0.00008*
P300 Fz ampl	7.30 6.40 (4.00–9.40) 4.49	5.69 5.75 (4.10–7.25) 2.82	0.190**
P300 Cz lat	321.6 326.0 (309.0–335.0) 23.1	348.4 352.5 (333.0–372.5) 32.3	0.00015*
P300 Cz ampl	8.30 8.30 (5.30–9.20) 4.26	7.26 7.45 (4.45–9.50) 3.64	0.271*
P300 Pz lat	324.1 324.0 (307.0–339.0) 24.1	350.5 353.0 (338.0–373.0) 30.6	0.00014*
P300 Pz ampl	8.60 7.60 (5.90–10.70) 4.18	8.52 8.25 (4.35–11.10) 4.71	0.944*

SLE – systemic lupus erythematosus; SD – standard deviation; NPSLE – neuropsychiatric systemic lupus erythematosus; SLEDAI – systemic lupus erythematosus Disease Activity Index; lat – latency; ampl – amplitude; Fz, Cz, Pz – points on the skull surface according to the International 10–20 system of EEG/SEP recording; * analysis of variance (ANOVA); ** Kruskal-Wallis test; p-values in bold are statistically significant.

Parameters	NPSLE subgroup (n = 16) median (quartiles)	Non-NPSLE subgroup (n = 21) median (quartiles)	p-value*	SLEDAI <6 (n = 11) median (quartiles)	SLEDAI >6 (n = 26) median (quartiles)	p-value*
N200 Fz lat	222.0 (203.5–247.0)	223.0 (210.0–226.0)	0.297	231.0 (223.0–253.0)	216.5 (203.0–233.0)	0.0580
N200 Fz ampl	4.80 (2.00–8.25)	5.20 (1.30–0.40)	0.854	5.20 (3.50–10.40)	4.70 (1.30–8.40)	0.506
N200 Cz lat	221.0 (198.5–244.5)	219.0 (210.0–226.0)	0.263	230.0 (215.0–251.0)	213.5 (198.0–233.0)	0.0650
N200 Cz ampl	3.85 (2.00–7.70)	4.20 (2.60–7.90)	0.759	5.20 (1.80–7.90)	3.85 (2.30–7.90)	0.842
N200 Pz lat	221.5 (200.5–253.0)	219.0 (210.0–228.0)	0.244	232.0 (215.0–270.0)	214.5 (200.0–233.0)	0.0753
N200 Pz ampl	2.70 (1.50–5.80)	4.00 (1.60–6.10)	0.783	2.90 (1.20–7.00)	3.60 (1.60–6.10)	0.947
P300 Fz lat	357.0 (334.0–374.0)	349.0 (332.0–358.0)	0.949	349.0 (319.0–378.0)	350.0 (334.0–363.0)	0.959
P300 Fz ampl	4.80 (3.40–7.20)	6.20 (4.90–7.30)	0.911	4.40 (4.40–7.30)	6.30 (4.40–7.20)	0.319
P300 Cz lat	356.0 (332.0–376.0)	350.0 (334.0–357.0)	0.974	352.0 (319.0–378.0)	353.0 (334.0–360.0)	0.945
P300 Cz ampl	5.40 (3.40–8.90)	8.90 (6.40–10.20)	0.531	4.30 (4.30–9.80)	8.40 (5.00–9.30)	0.303
P300 Pz lat	357.0 (339.0–376.0)	352.0 (337.0–356.0)	0.860	353.0 (321.0–376.0)	353.0 (339.0–364.0)	0.757
P300 Pz ampl	7.40 (3.60–10.20)	10.0 (7.6–12.6)	0.386	4.80 (4.80–10.20)	8.50 (6.70–11.60)	0.192

NPSLE – neuropsychiatric systemic lupus erythematosus; SLEDAI – systemic lupus erythematosus Disease Activity Index; lat – latency; ampl – amplitude; Fz, Cz, Pz – points on the skull surface according to the International 10–20 system of EEG/SEP recording; * Kruskal-Wallis test; p-values in bold are statistically significant.

antibodies (Fz: 360 ms, Cz: 362 ms and Pz: 364.3 ms vs 333.1 ms, 332.4 ms and 334.9 ms, respectively; $p = 0.01$). No other significant relationships were found between the ERPs parameters and immunological findings.

No correlations were found between the ERPs parameters and the duration of the disease, duration of CNS involvement in NPSLE patients or dose of corticosteroids.

Discussion

Neuropsychological assessment revealed CI (with at least 2 cognitive domains affected) in 35% of our SLE patients. A similar frequency of CI in the course of SLE was reported by some authors, while both higher and lower values were also described.^{2,4,9–15} Our patients showed impaired performance mainly within the domains of memory (especially verbal), verbal fluency, attention, and executive functions, with visuospatial skills apparently being least affected. These findings are consistent with some studies on the subject, although other authors have found a predominant decline in the visuospatial domain or have shown that all cognitive domains have been similarly compromised.^{11–20} Such a range of conclusions may be attributed to the different tests administered and the only recent application of specific nomenclature in this field in SLE.¹⁶ Therefore, we chose the tests from the battery recommended by ACR, where adequate normative data is available.¹

The majority of CI patients in our material fulfilled the criteria for NPSLE and they had a longer duration of CNS involvement than NPSLE subjects without CI. However, impaired cognitive performance (within at least 1 of the domains tested) was also found in non-NPSLE patients. Most authors agree that CI is more pronounced and more common in NPSLE, but may occur even in the absence of overt neurological and psychiatric symptoms.^{4,19–22} It is a matter of debate whether CI can appear irrespective of clinically diagnosed CNS involvement or perhaps may precede other NPSLE features.^{12,23}

Cognitive performance is claimed to be affected in its course by SLE activity and chronic CNS damage. We found higher SLEDAI scores in CI subjects, but without differences in the duration of the disease. Among particular neuropsychological tests, only the z-score for the delayed part of AVLT (a measure for long-term verbal memory) correlated significantly with the SLEDAI score. Systemic lupus erythematosus Disease Activity Index has been suggested as an independent predictor of CI and has been reported to correlate with the Global Cognitive Index as well as the tests measuring attention and executive domains.^{16,24} Although in some studies, the relationships between SLEDAI and cognitive performance have been denied, this may be attributed to the heterogeneity of SLE patients.¹³ The activity of the disease is associated with therapeutic strategies. All our patients were treated with corticosteroids, but no correlations were found

between the medication dosage and cognitive performance, which is consistent with the majority of studies in this field.^{4,13,15,17} Cognitive impairment has been described as a side effect of recent corticosteroid treatment, but its occurrence during regular corticosteroid use has been attributed rather to the severity of the disease itself than to any adverse effect of the medication.^{25,26}

Auto-antibodies and cytokines are immunological markers of SLE. In our SLE patients, APL (especially aCL), anti-nucleosome and anti-dsDNA antibodies were most frequently detectable. In other studies on this subject, APL antibodies are predominantly associated with CNS involvement, followed by anti-NR2 and anti-Rib-P antibodies.^{10,14,16} Anti-phospholipids are supposed to modulate neuronal function by reacting directly with neurons and affecting them via cerebrovascular insufficiency due to thrombosis.^{16,27} However, the relationships between the abovementioned auto-antibodies and cognitive functioning remain a contested issue. Some authors have observed associations between the presence and level of APL and CI,^{14,16,28,29} while others have not confirmed this.^{14–16,28–30} Similar discrepancies have been found in the case of anti-NR2 antibodies.^{10,13} We did not find any significant differences in terms of the immunological status between SLE patients with and without CI. However, we found some correlations between immunological findings and particular neuropsychological test results assessing non-verbal memory, attention, visuospatial skills, and executive functions. These findings seem especially interesting regarding aCL and anti-dsDNA antibodies, which were among the most frequently detected antibodies in the studied group. Similar associations between aCL and anti-dsDNA antibodies and the performance within visuospatial skills, attention and executive function domains were described by Conti et al. and Peretti et al.^{16,17} The presence of these antibodies in SLE patients might be indicative of subtle and more selective cognitive deficit, and thus be helpful in identifying patients requiring a closer follow-up in this field.

As many as 48% of our patients had recognized depression and 18 had BDI scores indicating mild or moderate depressive symptoms. As depression is one of common psychiatric manifestations of SLE and can potentially be a confounding factor in the assessment of cognitive performance, we considered this fact in the analysis of the data.^{13,31} We divided the patients into the NPSLE and non-NPSLE subgroups twice, including and not including depression in NPSLE criteria. For both versions, we obtained the same results regarding the correlations between cognitive performance, the ERPs results and the NPSLE status. We did not find significant relationships between the BDI results or the diagnosis of depression and neuropsychological or ERPs measures. Thus, the association between cognitive performance and depression in our SLE patients could be eliminated, as in the studies by Lapteva et al. and Cavaco et al.^{13,32}

The ERPs analysis in our SLE patients showed mainly abnormalities of the P300 component. P300 is considered

an electrophysiological index of global cognitive functioning and – as it is not a source specific potential – its abnormalities correspond best with generalized or multifocal CNS damage. Prolonged P300 latency in our SLE patients suggests slowed information processing, while lowered amplitude (found in some patients, although without significant differences of mean values between SLE subjects and controls) may be associated with attention and motivation impairment. Similar abnormalities in the P300 parameters have already been reported in SLE patients, with their frequency ranging from 35% to over 70%.^{3–6} Considering the mainly subcortical localization of CNS lesions in the course of SLE, one could expect more common abnormalities of the N200 component, which is attributed to early, subconscious stimulus processing. Prolonged latency of N200 was less commonly found in our patients than that of the P300 component. We also found, somewhat surprisingly, a trend for an increase in the N200 amplitude in patients in comparison to controls. It is possible that cognitive deficits in these patients made the ERPs task more effortful and caused increased attention concentration. Apart from the studies of Khedr et al., who found no N200 abnormalities in SLE patients, and Langosh et al., who reported decreased latency of the N100 component, using the mismatch negativity paradigm, early ERPs components have not been analyzed in SLE patients.^{4,33}

Although the mean values of the ERPs parameters did not differ between our NPSLE and non-NPSLE patients, prolonged N200 latency occurred more frequently in the former subgroup. This finding may be associated with the mainly subcortical CNS involvement in SLE mentioned above. In the studies on ERP, P300 abnormalities have mainly been described as typical for NPSLE patients, and thus differentiating them from non-NPSLE ones.^{3,4,6} We found a similar and rather high (over 60%) frequency of P300 abnormalities in both subgroups. Similar findings were reported by Mostafa et al., who also noticed that in 75% of patients with P300 abnormalities, but without clinical signs of CNS involvement, NPSLE developed during the 18 months of follow-up.³ Moreover, we did not ascertain significant relationships between the ERPs parameters and SLE-related variables, including the duration of the disease, SLEDAI score and corticosteroid dosage, or immunological findings, apart from slightly prolonged P300 latency in patients with an absence of anti-nucleosome antibodies. Thus, ERPs abnormalities may already occur in early and less active phases of SLE, and indicate subclinical CNS involvement, which suggests their potential predictive value.

The strength of our study is associated with simultaneous neuropsychological and electrophysiological assessment of cognitive functions in SLE patients, as well as their reference to the clinical and immunological markers of SLE. To our knowledge, there has been so far no study analyzing such a wide range of auto-antibodies regarding cognitive performance in SLE. The limited number

of patients and the fact that the assessment of cognition was performed only once may be considered the limitations of our study. Nevertheless, our findings, especially those concerning non-NPSLE patients, seem to encourage further investigation in this field, including follow-up of cognitive performance in SLE patients from the onset of the disease.

In conclusion, CI revealed by neuropsychological testing seems to be more closely related to the clinical and immunological features of SLE than ERPs abnormalities. However, ERPs are worth including as a complementary method in the assessment of cognitive performance in SLE patients. Cognitive impairment deserves attention as a specific aspect of CNS involvement in SLE, which should be evaluated from the early phase of the disease and monitored during its course.

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