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Cognitive functions and autoantibodies in patients with systemic lupus erythematosus

Funkcje poznawcze a autoprzeciwciała u chorych na toczeń rumieniowaty układowy

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Abstract

Introduction: Autoantibodies may occur in the course of various diseases. In the case of systemic lupus erythematosus the presence of specific autoantibodies is included in the classification criteria of the disease. **The aim of the study** was to investigate whether the presence of the serologic markers of systemic lupus erythematosus, i.e. anti-dsDNA, anti-Sm and anticardiolipin antibodies of the class IgM and IgG are linked with the results of neuropsychological tests evaluating selected cognitive functions in patients without overt neuropsychiatric lupus and without antiphospholipid syndrome. **Material and methods:** The study included 22 patients with systemic lupus erythematosus. For the assessment of anti-dsDNA, anti-Sm and anticardiolipin antibodies the immunoenzymatic method was used. For neuropsychological estimation of the selected cognitive functions the attention switching test and the choice reaction time were applied, in which the results are expressed as the average delay i.e. mean correct latency, using the computer-based Cambridge Neuropsychological Test Automated Battery (CANTAB). **Results:** The results of attention switching test in patients with anti-Sm antibodies were lower, but not significantly different from those obtained by the patients without such antibodies: 75.0 (73.12–88.12) *vs.* 92.5 (85–95). Choice reaction time was significantly longer in patients with anti-Sm antibodies in comparison to the patients without anti-Sm antibodies: 614.9 (520.6–740.8) *vs.* 476.7 (396.6–540) ($p = 0.01$). No significant difference was demonstrated in the results of attention switching test and choice reaction time with regard to the presence of anti-dsDNA antibodies. The results of attention switching test and choice reaction time were not different between the groups of patients with and without anticardiolipin antibodies in the IgM and IgG class. **Conclusions:** Anti-Sm antibodies seem to contribute to the pathogenetic pathway involved in the deterioration of the results of the selected cognitive functions in systemic lupus erythematosus patients. The use of neuropsychological assessment as a screening procedure in systemic lupus erythematosus patients with anti-Sm antibodies appears to be reasonable.

Key words: systemic lupus erythematosus, autoantibodies, cognitive functions

Streszczenie

Wprowadzenie: Autoprzeciwciała mogą występować w przebiegu różnych chorób. W przypadku tocznia rumieniowatego układowego obecność określonych autoprzeciwciał stanowi jedno z kryteriów klasyfikacyjnych choroby. **Celem pracy** było wykazanie, czy obecność serologicznych markerów tocznia rumieniowatego układowego, tj. autoprzeciwciał anty-dsDNA, anty-Sm oraz przeciwciał antykardiolipinowych klasy IgM i IgG, jest związana z wynikami testów neuropsychologicznych, oceniających wybrane funkcje poznawcze u pacjentów bez objawów tocznia neuropsychiatrycznego i bez zespołu antyfosfolipidowego. **Materiał i metody:** Badaniem objęto 22 chorych na toczeń rumieniowaty układowy. W badaniu przeciwciał anty-dsDNA, anty-Sm i przeciwkardiolipinowych wykorzystano metodę immunoenzymatyczną. Do oceny neuropsychologicznej wybranych funkcji poznawczych użyto testu przełączania uwagi i czasu reakcji wyboru, w którym wyniki są wyrażone jako średnie opóźnienie; wykorzystano komputerowy zestaw Cambridge Neuropsychological Test Automated Battery (CANTAB). **Wyniki:** Wyniki testu przełączania uwagi u pacjentów z przeciwciałami anty-Sm były niższe, ale nie różniły się znacząco od tych uzyskanych przez pacjentów bez tych przeciwciał: 75,0 (73,12–88,12) *vs* 92,5 (85–95).

Czas reakcji wyboru był istotnie dłuższy u chorych na toczeń rumieniowaty układowy z przeciwciałami anty-Sm w porównaniu z pacjentami bez tych przeciwciał: 614,9 (520,6–740,8) *vs* 476,7 (396,6–540) ($p = 0,01$). Nie wykazano istotnej różnicy w wynikach testu przełączania uwagi i czasu reakcji wyboru w zależności od występowania przeciwciał anty-dsDNA i przeciwciał przeciwkardiolipinowych klasy M i G. **Wnioski:** Przeciwciała anty-Sm wydają się przyczyniać do łańcucha patogenetycznego związanego z pogorszeniem wyników wybranych funkcji poznawczych u chorych na toczeń rumieniowaty układowy. Uzasadnione wydaje się przesiewowe zastosowanie badania neuropsychologicznego u chorych na toczeń rumieniowaty układowy z występującymi przeciwciałami anty-Sm.

Słowa kluczowe: toczeń rumieniowaty układowy, autoprzeciwciała, funkcje poznawcze

INTRODUCTION

Autoantibodies may occur in the course of various diseases (Hochberg, 1997; Merkel *et al.*, 1996; Nahass, 1997; Sène *et al.*, 2008). In the case of systemic lupus erythematosus (SLE) the presence of specific autoantibodies is included in the classification criteria of the disease. The classification criteria for SLE comprise the presence of anticardiolipin (aCL), anti-Sm and anti-dsDNA antibodies (Hochberg, 1997). Among them, aCL antibodies may contribute to the development of thrombotic disorders as a result of their interaction with negatively charged phospholipid-protein complexes, as well as platelets and endothelial cells (Roubey, 1998). Regarding the fact that the aCL antibodies contribute to the increased risk of thrombotic events, including those in the central nervous system, as a consequence they may contribute to the deterioration of functions of the nervous system, such as cognitive functions (Brey, 2000). On the other hand, there are reports on the possible role of aCL antibodies in the primary psychiatric disorders wherein these antibodies react with the target molecules on the surface of the cells of the nervous system (Sirota *et al.*, 2006). Therefore, it seems to be reasonable to search for the relationship between the occurrence of the selected autoantibodies and disorders within the central nervous system. However, not much attention has been paid to the study of the relationship between autoantibodies and cognitive functions in patients suffering from SLE without overt clinical manifestation of neuropsychiatric lupus or without antiphospholipid syndrome. Considering the fact that antibodies, especially aCL, occur in the course of various skin diseases, demonstration or exclusion of the relationship between them and the cognitive functions in such patients seems to be relevant for clinical practice. In the case of confirmation of such a link the obtained results would imply the need for neuropsychological assessment, and in justified cases, the introduction of cognitive training of the patients.

The aim of the study was to investigate, whether the presence of the serologic markers of SLE i.e. anti-dsDNA, anti-Sm and aCL antibodies of the class IgM and IgG is linked with the results of neuropsychological tests evaluating selected cognitive functions in patients without overt neuropsychiatric lupus and without antiphospholipid syndrome.

MATERIAL AND METHODS

The study included 22 patients with SLE, 21 female and 1 male, aged 27–62, mean 41.9 ± 9.5 years. The diagnosis was established on the basis of the classification criteria for SLE (Hochberg, 1997). The disease duration ranged from 3 to 24, mean 9.8 ± 5.8 years. The activity of SLE was less than 6 according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (Lam and Petri, 2005). The study was approved by the local Bioethics Committee (No. RNN/123/13/KB).

In order to detect autoantibodies in serum, blood was collected, centrifuged, and then the serum was stored at –70°C until the time of laboratory assessment. Antinuclear antibodies and their titer were determined using reagent kit of Immuno Concepts Colorzyme® ANA Test System (USA). In order to evaluate the serological markers of SLE such as antibodies against anti-double-stranded DNA (dsDNA) and Sm antigen, immunoenzymatic method was applied, using ELISA QUANTA Lite® dsDNAkit (INOVA, USA) and INOVA QUANTA Lite® Sm ELISA (INOVA, USA). For the indication of aCL antibodies of the IgG and IgM class, reagent kits of AUTOSTAT II ACA IgM and IgG (Hycor, USA) were used.

In neuropsychological evaluation the Cambridge Neuropsychological Test Automated Battery (CANTAB) was used, which is a computer-based method. Tests in CANTAB are based on non-verbal tasks displayed on the computer screen, and require motor, non-verbal answers provided on the touch screen of the computer. Therefore, CANTAB represents a valuable option in the psychological evaluation of patients, regardless of their language skills, and allows a comparison of results between groups of patients which are culturally and linguistically different. In our study two tests were used: a test of switching attention (attention switching task, AST), in which the results are expressed as the percentage of correct responses (%) (percent correct trials), and a test examining response time (choice reaction time, CRT), in which the results are expressed as the average delay (mean correct latency). Exclusion criteria for the neuropsychological study were: lack of cooperation with the patient, clinical symptoms of neuropsychiatric lupus, clinical symptoms of antiphospholipid syndrome, psychotic symptoms, the use of psychoactive substances. Twenty-five patients participated

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Sign	Number of patients (percentage)
Malar rash	12/22 (54%)
Discoid rash	4/18 (22%)
Oral erosions	3/22 (13%)
Photosensitivity	13/22 (59%)
Arthritis	21/22 (95%)
Pleuritis or pericarditis	1/22 (4%)
Renal disorder	2/22 (9%)
History of neurological disorder	0/22 (0%)
Haematological disorder	18/22 (81%)

*Tab. 1. Clinical characteristic of patients with SLE (*n = *22)*

in the psychological assessment with CANTAB following the application of the exclusion criteria.

The results were analyzed with Statistica Version 10 software. For descriptive statistics median, upper and lower quartiles were used. For comparing the results of psychological tests between two groups of patients (with or without the specific antibodies), the Mann–Whitney *U* test was used. In all calculations $p < 0.05$ was regarded as statistically significant.

RESULTS

Clinical characteristics in patients with SLE is shown in Tab. 1.

The results of specificity of autoantibodies in patients with SLE are shown in Tab. 2.

The results of attention switching test in patients with anti-Sm antibodies were lower, but not significantly different from those obtained by patients without such antibodies: 75.0 (73.12–88.12) *vs.* 92.5 (85–95).

Choice reaction time was significantly longer in patients with anti-Sm antibodies in comparison to patients without such antibodies: 614.9 (520.6–740.8) *vs.* 476.7 (396.6–540) ($p = 0.01$) (Fig. 1).

In SLE patients with anti-dsDNA antibodies no significant difference was demonstrated in the results of attention switching test in comparison to patients without such antibodies: 92.1 (83.4–93.4) *vs.* 90.6 (85–95.6).

The results of choice reaction time in SLE patients with anti-dsDNA did not significantly differ from those obtained in the group without anti-dsDNA antibodies: 377.6 (358.6–568.7) *vs.* 498.8 (461.7–580.8).

There was no significant difference in the results of attention switching test between patients with SLE with aCL antibodies in the class IgM and without these antibodies: 90 (83.7–95) *vs.* 93.1 (88.1–94.3).

The choice reaction time did not differ significantly between patients with SLE with aCL antibodies in the IgM class and patients without these antibodies: 487.1 (402.5–580.8) *vs.* 505.8 (461.7–578.8).

In patients with SLE with aCL antibodies in the IgG class there was no significant difference in the results of attention switching test in comparison to patients without these antibodies: 91.5 (85–95.6) *vs.* 91.5 (66.5–94.6).

Specificity of autoantibodies	Number of patients (percentage)
Anti-Sm	5/22 (22%)
Anti-dsDNA	4/22 (18%)
aCL IgM	13/22 (59%)
aCL IgG	14/22 (63%)

*Tab. 2. Antibodies in patients with SLE (*n = *22)*

The choice reaction time did not significantly differ between SLE patients with aCL antibodies in the IgG class and without these antibodies: 496.4 (380–623.6) *vs.* 487.3 (466.6–549.7).

DISCUSSION

Immunological disorders manifested by the presence of autoantibodies, such as anti-Sm, anti-dsDNA and aCL antibodies constitute a classification criterion of SLE (Isenberg, 2010). Autoantibody production, deposition of immune complexes, production of inflammatory mediators, and subsequent cytotoxic neuronal damage, along with the prothrombotic status play a relevant role in the pathogenesis of organ lesion in SLE, especially in the development of neuropsychiatric lupus (neuropsychiatric SLE – NPSLE) (Meszaros *et al.*, 2012; Popescu and Kao, 2011). While various autoantibodies are detected in patients with neuropsychiatric lupus, only a limited number of them are directed against antigens of the nervous system. Several lines of evidence have indicated neuropsychiatric SLE to be associated with neuronal antigens, gangliosides, neurofilaments, glial fibrillar acidic protein, BRA (brain-reactive antibodies), MAP-2 (microtubule-associated protein 2) and NMDA (*N*-methyl-D-aspartate receptors) (Denburg *et al.*, 1987; Kinnunen *et al.*, 1993; Martinez *et al.*, 1992; Sanna *et al.*, 2000; Tin *et al.*, 2005; Williams *et al.*, 2004). A group of antigens also associated with neuropsychiatric lupus, but non-specific for neural

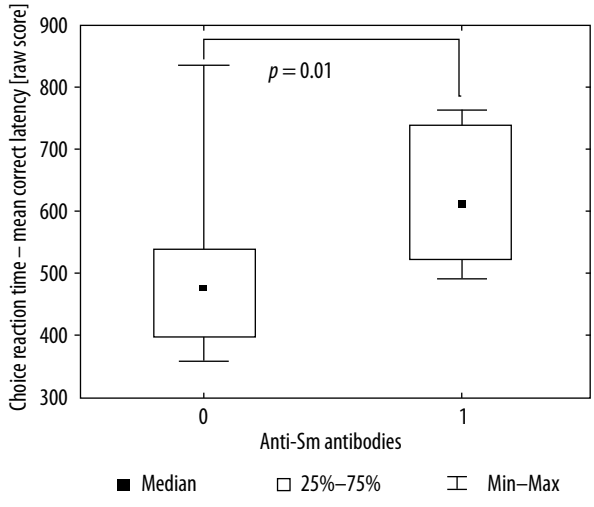

Fig. 1. Choice reaction time in SLE patients with and without anti-Sm antibodies

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tissue, are lupus anticoagulant, Sm, β_2-glycoprotein I, endothelial cell antigens, phospholipids, Ro, ribosomal protein P and NEDD-5 (Denburg *et al.*, 1987; Eber *et al.*, 2005; Margutti *et al.*, 2005; Mikdashi and Handwerger, 2004; Shimojima *et al.*, 2005; Song *et al.*, 2000). The aim of our study was to determine whether the presence in the serum of serologic markers for SLE, such as anti-dsDNA, anti-Sm, and aCL antibodies are associated with cognitive functions of patients with SLE without symptoms of neuropsychiatric lupus and without antiphospholipid syndrome. Cognitive functions were examined with the computer-based CANTAB in patients without symptoms of neuropsychiatric lupus or antiphospholipid syndrome. So far, only one study conducted by Calderón *et al.* (2014) used the CANTAB in the evaluation of neuropsychological patients with SLE. The authors did not demonstrate a significant difference in the frequency of presence of anti-dsDNA antibodies between patients with SLE with cognitive deficits in comparison to patients without this disorder (Calderón *et al.*, 2014). We have not confirmed any link between the presence of anti-dsDNA autoantibodies and the results of attention switching test and choice reaction time. In our study, only anti-Sm antibodies were associated with longer choice reaction time. The results of choice reaction time test reflect the overall attention of the patient and the speed of his/her motor skills. Undoubtedly, this test does not reflect the full range of cognitive functions, which span attention, logical reasoning, memory, ability to plan, organize and make decisions, spatial organization, language fluency and vocabulary, nor the rate of cognitive processes. Therefore, there is a need for further research with the use of other tests for the assessment of other components of cognitive functions. However, it may be concluded that anti-Sm antibodies can contribute to the pathogenetic chain associated with the deterioration of at least some cognitive functions in patients with SLE. Reiff *et al.* (1997) tested 11 children with symptoms of neuropsychiatric SLE, finding anti-Sm antibodies to be present in 36% of the patients. It may be speculated that in the case of patients with SLE with the presence of anti-Sm antibodies it would be reasonable to apply neuropsychological tests as a screening procedure. Unfortunately, the molecular mechanisms responsible for the relationship between anti-Sm antibodies and neuropsychiatric symptoms remain not fully explained. Sm antigen consists of at least 4 proteins: B (28 kDa), B1 (29 kDa), D (19 kDa), and E (13 kDa) (Cozzani *et al.*, 2014). Despite the marker role of anti-Sm antibodies in the classification criteria of SLE, the levels of anti-Sm antibodies frequently remain static throughout the clinical course of the disease (Pisetsky, 2012). It is different from the well-documented clinical usefulness of the determination of anti-dsDNA antibodies in monitoring the course of SLE, where the titer of anti-dsDNA antibodies can fluctuate depending on the activity of the disease and the occurrence of renal changes (Pisetsky, 2012). In contrast to anti-Sm antibodies, in our study the occurrence of anti-dsDNA antibodies was not associated with CANTAB results of attention switching test and choice reaction time. Unlike anti-Sm antibodies, the role of anti-dsDNA antibodies in the pathogenesis of SLE seems to be more specific. Kotzin and Kozora (2001) suggested that anti-DNA antibodies might cross-react with glutaminian NMDA receptor, thereby contributing to the neuronal damage. There is, however, a need for further studies on the molecular characteristics of target antigens and cross-reacting with anti-dsDNA and anti-Sm antibodies within the central nervous system. Another group of autoantibodies involved in the pathogenesis of SLE are aCL antibodies. These antibodies can interact with the negatively charged phospholipid-protein complexes, platelets, and endothelial cells, and may lead to the development of thrombotic lesions in the central nervous system (Roubey, 1998). In our group of SLE patients with no overt signs of neuropsychiatric lupus, aCL antibodies in the IgG class were detected in 54% of the patients, whereas in the IgM class in 38%. We have not shown a significant association between the occurrence of aCL antibodies and the results of attention switching test and choice reaction time. A limitation of our study was the examination of only patients suffering from SLE without overt neuropsychiatric symptoms. Therefore, we could not compare patients with SLE and ones with neuropsychiatric SLE. The impact of other factors involved in the pathogenesis of neuropsychiatric lupus should also be taken into account, including selected cytokines, such as interleukin (IL)-1, IL-6, IL-10, and interferon-γ, whose levels may be increased in the cerebrospinal fluid of patients with NPSLE (Svenungsson *et al.*, 2001; Trysberg *et al.*, 2004). On the other hand, the role of atherosclerosis in the course of SLE, and its influence on cognitive functions need not be underestimated, as in this group of patients the "lupus pattern" of dyslipoproteinemias may be found, manifesting by a reduced HDL fraction and an elevated triglyceride fraction, with a normal or slightly elevated level of LDL (Frostegård, 2005). Hence, there is a need for further studies regarding the impact of numerous, sometimes independent variables on the pathogenesis of lupus and cognitive functions.

CONCLUSIONS

Anti-Sm antibodies appear to contribute to the pathogenetic pathway involved in the deterioration of the selected cognitive functions in SLE patients. The use of neuropsychological assessment as a screening procedure in SLE patients with anti-Sm antibodies appears to be reasonable.

Conflict of interest

The authors do not report any financial or personal relationships with other persons or organizations that could adversely affect the content of the publication and lay claim to this publication.

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