Paper

Prevalence, involved domains, and predictor of cognitive dysfunction in systemic lupus erythematosus

Lupus
0(0) 1–9

DOI: 10.1177/0961203320958061
journals.sagepub.com/home/lup
SAGE

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Abstract

Background: Cognitive Dysfunction (CD) can occur in Systemic Lupus Erythematosus (SLE) before the occurrence of Neuropsychiatric Lupus Erythematosus (NPSLE). Given the reversibility and fluctuation of SLE-related CD, the research for possible predictors is of great significance for early detection and intervention.
Objective: We sought to determine the prevalence, involved domains, and possible predictors of CD in SLE patients.
Methods: We conducted a retrospective cross-sectional study at Nanfang Hospital from 2018 to 2019. A total of 78 SLE patients were recruited. The Montreal Cognitive Assessment (MoCA) scale was used to screen cognitive function. Demographic, clinical, and laboratory characteristics were collected. The serum anti-methyl-d-aspartate receptor (anti-NMDAR) antibody and S100β were measured by enzyme-linked immunosorbent assay (ELISA). Multivariate logistic regression analysis and ROC curve were used to assess the predictor of SLE-related CD.
Results: Of 78 recruited patients,53 (67.9%) had CD. It mainly involved delayed recall, abstract generalization, verbal repetition, and fluency. The disease activity index (SLEDAI) was not associated with SLE-related CD ($p > 0.05$). Multivariate logistic regression showed that an increase in each year of education there was a decrease in the likelihood of CD (OR 0.261, CI 0.080-0.857, $p = 0.027$) whereas with each unit increase in serum anti-NMDAR antibody there was an increased likelihood of SLE-related CD (OR 1.568, CI 1.073–2.292, $p = 0.020$).
Conclusion: The prevalence of SLE-related CD was 67.9% in our study and SLE-related CD was not associated with disease activity. Serum anti-NMDAR antibody can be used as a predictor for SLE-related CD.

Keywords

Systemic lupus erythematosus, cognitive dysfunctionpredictor, anti-NMDAR antibody

Date received: 13 March 2020; accepted: 19 August 2020

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic and heterogeneous immune disease, which can affect the nervous system. In 1999, the American College of Rheumatology (ACR) first defined 19 neuropsychiatric symptoms for neuropsychiatric systemic lupus erythematosus (NPSLE). Cognitive dysfunction (CD) is one of the most common clinical manifestations of NPSLE.[1] Previous research studies[2,3] suggest that CD can occur in SLE before it develops into NPSLE, and can manifest as a mild cognitive impairment to severe dementia which affects the patients' quality of life. Due to the absence of uniform screening methods, the reported prevalence varies from 20% to 80%.[4] Furthermore, previous studies[4,5] have shown that anti-methyl-d-aspartate receptor (anti-NMDAR) antibody and S100β protein are associated with SLE-related CD.

NMDAR is one of the ion-type glutamate receptor subtypes, mainly composed of NR2a, NR2b subunits, which participate in synaptic remodeling. On the one

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hand, NMDAR can promote cellular learning and memory by synaptic plasticity; on the other hand, NMDAR antibody response can strengthen the excitatory postsynaptic potential and mitochondrial permeability transition, cause Ca^{2+} overload and neuron apoptosis, eventually leading to the CD.[4] Specifically, the binding of the NR2A antibody to NMDAR promotes the survival of neurons and has a protective effect on neurons. Binding of NR2B antibody to NMDAR can lead to excitatory toxicity and increase neuron apoptosis.[6]

S100β is a calcium-binding protein secreted mainly by astrocytes in brain tissue. When an acute brain injury occurs, S100β is used as a neurotrophic factor to promote the differentiation and proliferation of astrocytes and the survival of neurons; when it is overproduced, it will aggravate the death of neurons, so the high level of S100 β protein has been considered to be a biomarker of brain injury and blood-brain barrier (BBB) damage.[5]

However, there are also conflicting findings and there is a scarcity of data from China. Thus, the main aim of our study was to investigate the prevalence, involved domains, and possible predictors of SLE-related CD, to provide a theoretical basis for the early detection and diagnosis of SLE-related CD.

Subjects and methods

This cross-sectional, retrospective study was conducted in the Department of Dermatology and Rheumatology, Nanfang Hospital of Southern Medical University during 2018–2019. All included SLE patients aged between 13 and 55 years and fulfilled the 1997 ACR diagnosis criteria for SLE.[7] 20 healthy controls were matched with gender, age, and education level of SLE patients. Exclusion criteria included other cognitive related diseases (stroke, vascular dementia, primary psychosis, and primary neurodegenerative diseases) or with data loss, neuropsychiatric symptoms caused by infection, electrolyte disorder, metabolism, uremia, and drugs. The disease activity was evaluated by the SLE Disease Activity Index 2000 (SLEDAI-2k).[8] Participants were divided into CD SLE group, non-CD SLE group, and healthy controls. All the participants have signed the informed consent form.

Data collection

All subjects underwent a structured interview to collect information on their socio-demographic characteristics including age, gender, years of education, and clinical manifestations. Information on specific clinical symptoms and laboratory tests were obtained from their medical records. Furthermore, the Montreal Cognitive Assessment (MoCA), the self-rating anxiety scale (SAS) and self-rating depression scale (SDS) were used to evaluate cognitive functions, anxiety, and depression, respectively.[9,10]

MoCA. MoCA is a brief 30-point screening instrument for CD. If the duration of education is less than 12 years, adding 1 point to the test results correct the bias of education level. The MoCA test showed the highest correspondence with the gold standard—ACR comprehensive battery (AUC = 99.4%, $P < 0.001$), sensitivity 84%, and specificity 100%.[11] The Chinese version of the MoCA is used widely and is validated and reliable.[12] It is easy to implement in clinical work because the whole process takes only 10–15 minutes. The MoCA assesses visuospatial/executive function, naming, attention, delayed recall, language, abstraction, and orientation.[9] Based on the diagnosis of SLE as defined by ACR in 1997, then according to MoCA, we defined a score $\geq$26 considered non-CD SLE group; while the score <26 represented CD SLE group. The higher the score, the better the cognitive function. All participants were instructed by a trained and qualified physician to complete the cognitive test.

SAS and SDS

SAS and SDS were used to evaluate their emotional state in the past 1 week. Scores of 20 items were added together to get rough scores, which were then multiplied by 1.25 to get standard scores. For the Chinese population, a score of 40 is indicative of anxiety.[11] And recent study recommends the use of an SDS raw score of 50 as the cut-off point for clinical significance.[13]

Laboratory related evaluation

All patients enrolled received routine standard examinations. The test results were from the Laboratory Department of Nanfang Hospital of Southern Medical University. Besides, anti-NMDAR antibody and S100βlevels in serum were determined by ELISA in our study according to the manufacturer's protocols (Meimian Industrial Co. Ltd, Jiangsu, China).

Statistical analysis. Continuous data are presented as mean ± standard deviation (SD) or median, the independent *t*-test or Mann-Whitney U test was used. Chi-square test or Fisher exact test was applied for categorical variables, which are expressed as counts or percentages. One-Way ANOVA and post-hoc Bonferroni or Dunnett T3's multiple comparisons were used to analyze differences among the three groups. Only variables showing statistically significant

in the univariate analysis were included in the multivariate logistic regression analysis. A p value < 0.05 was considered to be statistically significant. Analyses were conducted using SPSS version 22 (SPSS Inc., Chicago, Illinois, USA) and GraphPad 7.0 (La Jolla, CA, USA).

Results

Prevalence and involved domains of SLE related CD

A total of 78 patients with SLE were included, 69 females (88.5%) and 9 males (11.5%). According to the score of MoCA, 53 patients (67.9%) were found to have CD while others were not. The most commonly affected domains were delayed recall (80.5%), abstract generalization (79.2%), verbal repetition, and fluency (76.6%). The results showed that the CD SLE group obtained significantly lower scores in MoCA, visuospatial, executive functioning, naming, attention, language, abstraction, and delayed recall domains (Table 1). And there was no statistically significant difference between the non-CD SLE group and the healthy group.

General characteristics of patients

Compared to the non-CD SLE group the participants in the CD SLE group were older($p = 0.005$), have higher age of onset($p = 0.02$), and less years of education($p < 0.001$) (Table 2). There was no significant difference between the two groups about factors, such as anxiety, depression, and SLEDAI.

Immunological tests

The anti-dsDNA level in the CD SLE group was within the normal range, while the median anti-dsDNA level in the non-CD SLE group was higher than the normal upper limit (24 U/ml). The difference between the two groups was statistically significant ($P < 0.05$). The level of complement C4 in both groups was within the normal range, and the value of the non-CD SLE group was lower than that of the CD SLE group, with a statistically significant difference (Table 3). We found there were significant differences in serum anti-NMDAR antibody levels, but not in S100β levels (Table 4).

Predictors of CD in SLE

The variables with statistical significance (age, years of education, age at onset, complement C4, anti-dsDNA, anti-NMDAR antibody level) in univariate analysis were included in multivariate logistic regression analysis. Then we drew a ROC curve to assess the value of

Table 1. The tests of cognitive evaluation.

Group	MoCA	Visuospatial/ executive functions	Naming	Attention	Language	Abstraction	Delayed memory	Orientation
CD SLE group (n = 53)	20.40 ± 3.54	2.96 ± 1.34	2.31 ± 0.88	4.12 ± 1.42	1.38 ± 0.80	0.48 ± 0.67	2.77 ± 1.22	5.62 ± 0.89
Non-CD SLE group (n = 25)	27.32 ± 1.52	4.52 ± 0.92	2.88 ± 0.33	5.64 ± 0.64	2.56 ± 0.58	1.28 ± 0.74	4.36 ± 0.81	5.72 ± 0.54
Health controls (n = 20)	25.95 ± 3.15	4.10 ± 0.79	2.80 ± 0.41	5.05 ± 1.36	2.40 ± 0.68	1.35 ± 0.75	3.75 ± 0.91	5.95 ± 0.22
F value	52.079	17.955	7.347	12.828	28.334	16.841	20.319	1.576
P value	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.212

Table 2. The General characteristics of SLE patients.

Variables	CD SLE group N = 53 (%)	Non-CD SLE group N = 25 (%)	T/Z/X^2	P
Demographics				
Age (y)	34.40 ± 11.94	26.92 ± 9.70	–2.944	0.005
Sex (%) (female:male)	49 (91.7):4 (8.3)	20 (80):5 (20)	1.505	0.220
Time of education(y)	8.70 ± 3.20	11.96 ± 3.28	–4.167	0.000
BMI (kg/m^2)	21.52 ± 3.31	21.96 ± 3.57	–0.539	0.592
Disease duration (m)	68 (23.5,113)	36 (11.5,96)	–1.403	0.160
Age at onset (y)	27.85 ± 10.24	21.96 ± 10.11	–2.380	0.020
The first SLEDAI	10 (6,15.5)	10 (6,18.5)	–0.791	0.429
SLEDAI this time	4 (0,8)	4 (0,13.5)	–0.148	0.882
A history of NPSLE	5 (9.4)	5 (20):20 (80)	0.883	0.347
Complicated with lupus nephritis	29 (54.7)	15 (60):10 (40)	0.193	0.661
Number of diagnostic criteria	5 (4,6)	5 (4,5)	6.813	0.178
Emotion assessment				
Anxiety	11 (20.8)	8 (32)	2.214	0.662
Depression	24 (45.3)	7 (28)	3.181	0.363
Clinical manifestations				
Butterfly erythema	36 (67.9)	17 (68.0)	0.000	0.995
Discoid rash	2 (3.8)	1 (4.0)	0.000	1.000
Photosensitivity	14 (26.4)	6 (24.0)	0.052	0.820
Hair loss	20 (37.8)	14 (56.0)	2.305	0.129
Fever	11 (20.8)	10 (40.0)	3.198	0.074
Oral ulcer	5 (9.4)	5 (20.0)	0.883	0.347
Arthritis	34 (64.2)	18 (72.0)	0.471	0.493
Serositis	14 (26.4)	3 (12.0)	2.071	0.150
Muscle pain	3 (5.7)	3 (12.0)	0.276	0.599
Finger vasculitis	11 (20.8)	4 (16.0)	0.036	0.850
Laboratory tests				
Triglyceride (mmol/l)	1.17 (0.82,1.69)	0.97 (0.85,1.27)	–0.635	0.525
Cholesterol (mmol/l)	4.49 (3.68,5.43)	4.41 (3.96,5.66)	–0.676	0.499
CRP (mg/l)	0.66 (0.36,4.31)	2.89 (0.29,3.52)	–0.205	0.838
ESR(mm/1h)	15 (8,36)	14 (11,100)	–0.795	0.426
Urinary protein (g/d)	0.48 (0.11,1.44)	0.59 (0.14,3.54)	–0.160	0.873
Medicine use				
Current prednisone (mg/d)	20 (15.00,34.15)	25 (15,45)	–0.776	0.438
Maximum prednisone (mg/d)	50 (47.5,55.0)	50 (50,60)	–0.996	0.319
Immunosuppressant (g/d)	0 (0,1)	0 (0,1.5)	–1.195	0.232
Accumulated CTX (g)	0 (0,4.35)	0 (0,5.5)	–0.147	0.883
Hydroxychloroquine(g/d)	0.2 (0,0.4)	0.4 (0,0.4)	–0.746	0.456

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CTX: cyclophosphamide.

anti-NMDAR antibody level in the diagnosis of SLE-related CD (Figure 1). We found that The AUC was 0.805 ($P < 0.01$), 95% CI: 0.667-0.943. When the anti-NMDAR antibody level is 9.550pg/ml, the maximum Youden index is 0.533, which is the best for the diagnosis of SLE with CD, with a sensitivity of 73.3% and a specificity of 80%.

Discussions

In recent years, it has been reported that in patients with SLE the relative risk of CD was greater than that of rheumatoid arthritis (RA) and healthy controls.[9] The pathogenesis of SLE-related CD involves comprehensive factors such as autoantibodies, an inflammatory protein, cytokines and BBB destruction, which lead to cerebrovascular diseases and neurotoxicity.[14–19] To our knowledge, little is known about the prevalence, involved domains, and possible predictors in China.

Cognition and emotion

We used the MoCA scale to assess the patients' cognition and found 67.9% of patients had a CD which is within the reported range of 20–80%.[6] The CD SLE

Table 3. The laboratory immunological related data.

Variables	CD SLE group n = 53(%)	Non-CD SLE group n = 25 (%)	Z/F/T	P
ANA(U/ml)	224.10 (51.22,300.00)	300 (28,300)	−1.300	0.194
Anti-dsDNA(U/ml)	8.83 (2.84,52.01)	65.13 (6.62,142.92)	−2.580	0.010
Anti-Sm(U/ml)	5.45 (3.73,10.62)	3.81 (2.67,6.61)	−0.830	0.406
Anti-Sm/RNP	10.92 (3.26,147.75)	16.55 (2.93,178.08)	−0.234	0.815
C3 (g/l)	0.81 ± 0.30	0.76 ± 0.34	0.741	0.461
C4 (g/l)	0.17 ± 0.10	0.12 ± 0.76	2.309	0.024
CH50(U/ml)	37.75 ± 17.07	32.78 ± 19.74	1.142	0.257
aCL-IgG(GPL/ml)	0.94 (0.52,1.72)	0.90 (0.64,2.66)	−0.821	0.412
aCL-IgM(MPL/ml)	0.49 (0.22,1.00)	0.72 (0.23,1.32)	−1.279	0.201
Anti-SSA	34 (64.2)	15 (62.5)	0.019	0.889
Anti-SSB	10 (18.9)	3 (12.5)	0.131	0.717
AHA	17 (32.1)	10 (41.7)	0.667	0.414
AnuA	16 (30.2)	9 (37.5)	0.404	0.526
AMA	2 (3.8)	1 (4.2)	0.000	1.000
Ro52	21 (39.6)	9 (37.5)	0.031	0.860
Anti-U1-RNP	25 (47.2)	11 (45.8)	0.212	0.913
Anti Jo-1	2 (93.8)	0	0.918	0.338
Anti Scl-70	0	0	\	\
ARPA	20 (37.7)	7 (29.2)	0.533	0.465

ANA: antinuclear antibodies; C: complement; aCL: anticardiolipin antibodies; AHA: antihistone antibodies; AnuA: Antinucleosome antibodies; AMA: antimitochondrial antibodies; RNP: Ribonucleoprotein;ARPA: antiribosomal P protein antibodies.

Table 4. The level of anti-NMDAR antibody and S100β protein.

Variables	CD SLE group n = 53	Non-CD SLE group n = 25	Healthy controls N = 20	F	P
Anti-NMDAR antibody (pg/ml)	12.29 ± 5.30	8.23 ± 1.77	8.82 ± 3.48	8.175	0.001
S100β protein (pg/ml)	827.94 ± 368.37	785.62 ± 448.83	530.55 ± 433.25	0.597	0.554

group had a poor performance in visuospatial and executive function, naming, attention, language, abstraction, and delayed recall compared to non-CD SLE and healthy groups. The most commonly affected domains were delayed recall (80.5%), abstract generalization (79.2%), language repetition and fluency (76.6%) in our study contrast to Tomietto et al.[20] study showing that the most involved fields were memory (50%), complex attention (42.3%) and executive function (26.9%). Interestingly, the MoCA score of a healthy group is slightly lower than the cut-off value and than that of the non-CD SLE group score. CD can occur in both SLE and the healthy group. However, the relative risk of CD in SLE was greater when compared to RA and healthy individuals; relative risk being 1.80 and 2.80, respectively.[9] With similar years of education in healthy and SLE group we found overall low level in years of education averaging 9 years. CD SLE group, we found that their performance was significantly worse; while the non-CD SLE group, their performance was similar to that of the healthy group, and their MoCA scores were close to the normal level of 26 points, and the difference was not statistically significant. Many studies[21,22] did not include a healthy group when using MoCA as the cognitive battery. In this regard, we still need more data to further confirm the cognitive performance of the non-CD SLE group and the healthy group. Besides, more scholars have paid attention to anxiety and depression in SLE patients. Moreover, previous study[23] found that fragmented sleep and depression can increase the incidence of CD. And only depression levels, among clinical variables, significantly predicted cognitive performance by multivariate analysis.[24] Anxiety and mood disorder were also mentioned in the NPSLE classification standard formulated by ACR in 1999.[1] However, we found that patients diagnosed with NPSLE were often in a serious condition and could not cooperate with the cognitive evaluation. Therefore, our research did not include these patients. Our study found that the anxiety and depression symptoms scores of the CD SLE group were higher than those of the non-CD

Table 5. The effect of multivariate logistic regression analysis.

Variables	B value	S.E	Wald	P	OR	95%CI
Years of education (y)	−1.342	0.606	4.902	0.027	0.261	0.080–0.857
Anti-NMDAR antibody (pg/ml)	0.450	0.194	5.402	0.020	1.568	1.073–2.292

SLE group, but the difference was not statistically significant. One of the reasons may be that although the scores of emotional scale completed by the patients at that time could avoid memory bias, they could not represent the level of anxiety and depression in the whole course of the disease and were underestimated; secondly, the sample size was still limited. Efforts should be made to continue to study this social-psychological issue in the context of multidimensional aspects.

Immunological factors

In this study, we found that the elevated level of serum anti-NMDAR antibody was a predictor of SLE-related CD (OR = 1.568, 95%CI:1.073–2.292, $P < 0.05$) (Table 5). The area under the curve (AUC) was 0.805 (95%CI: 0.667–0.943). When the anti-NMDAR antibody level is 9.550 pg/ml, the maximum Youden index is 0.533, which is the best for the diagnosis of SLE with CD, with a sensitivity (true positive rate) of 73.3% and a specificity (true negative rate) of 80%, suggesting that human serum anti-NR2 antibodies have a certain value in the diagnosis of SLE-related CD. And the previous study[25] has also indicated that SLE-related CD is associated with anti-NMDAR antibodies. Meta-analysis by Tay et al.[4] found that the pooled incidence of increased serum anti-NR2A/2B antibody was 24.6% (95%CI:18.5%–32%) in SLE, 19.7% (95%CI:11.8%–31.0%) in Sjogren's syndrome, 14.5% (95%CI: 2.2%–56.9%) in disease control group, and 7.6% (95% CI:4.6%–12.4%) in healthy group ($P = 0.001$). Omdal et al.[26] found that the anti-NR2 antibody was significantly correlated with behavioral abnormalities, depression, decreased short-term memory, and learning ability in SLE patients. However, in our study, the level of anti-dsDNA and C4 were associated with SLE-related CD in univariate analysis alone but not in multivariate analysis. But on the other hand, we know that the anti-dsDNA antibody is an indicator of SLE activity, and the lower the C4 level, the more it reflects disease activity. The value of anti-dsDNA and C4 in the non-CD SLE group showed higher disease activity. It is speculated that there was no linear relationship between the disease activity and the occurrence of SLE-related CD. Besides, no other autoantibodies such as ARPA and aCL were found to be associated with the cognitive function of SLE. The previous study[27] suggested that the continuous increase of aCL was significantly correlated with the decrease of word fluency, concentration, attention, and reaction time. Gonzalez et al.[17] indicated that ARPA was associated with impaired executive planning and decreased attention in SLE patients. The possible mechanism is that ARPA interacts with neuronal surface P antigen to increase apoptosis induced by Ca^{2+} influx of primary cultured or human cortical and hippocampal neurons and interfere with glutamine-mediated synaptic remodeling. As for the inconsistent data, we considered that antibody and cognitive function can fluctuate with time, and their real corresponding changes cannot always be captured in the investigation time. Perhaps, only persistent antibody positivity can explain its association with cognitive function; there can be methodological differences, antibody detection, and the selection of subjects. The presence of autoantibodies in the brain could not be confirmed as CSF was not used and we do not have any measures of BBB integrity. Therefore, further large sample and longitudinal cohort studies are needed to further explore the changes in cognitive function and antibody levels in serum and CSF as well as the destruction of BBB over time, to confirm our conclusions.

Inflammatory factors

Previous study[28] have reported that chronic inflammation can lead to neurodegenerative diseases, such as multiple sclerosis, Alzheimer's disease, acquired immune deficiency syndrome, and so on. In our study, the inflammatory factors such as CRP, ESR, S100β showed no association with SLE-related CD. However, previous study[29] reported increased S100βlevels was observed in adult SLE patients. And Lapa et al.[5] found S100β is associated with cognitive impairment in childhood-onset SLE patients (OR:3.7, 95%CI:1.2–7.1, $p = 0.028$). It is considered that serum S100β protein can also be released by damaged tissues outside the brain or unknown and insidious neurodegenerative diseases. Besides, SLE-related CD may not be caused by merely bacteria and viruses that can lead to an increase in the CRP or ESR level. Hsu-ko Kuo et al.[30] indicated through systematic evaluation that a high level of CRP is not only a risk factor for cardiovascular disease, but also correlated with cognitive impairment, suggesting that a high level of CRP in serum can predict cognitive decline and the occurrence

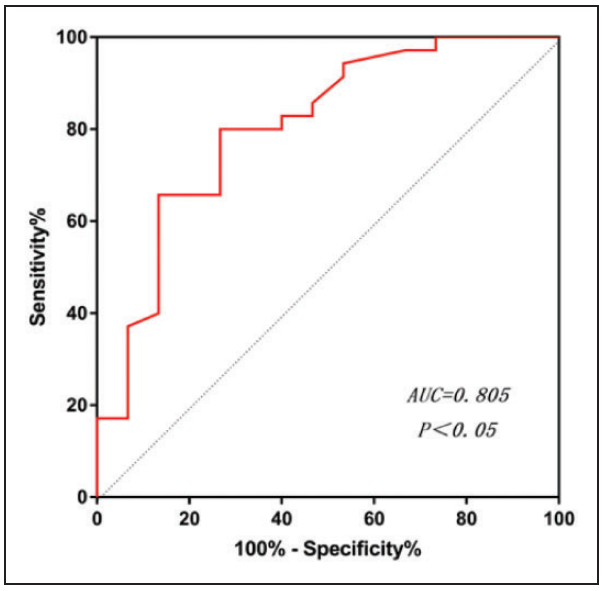

Figure 1. ROC curve of serum anti-NMDAR antibody.

of dementia. The previous study[19] stated that CRP and high-sensitive CRP (hs-CRP) were the same substance, but there were differences in the detection kit, detection method, sensitivity, detection of the lower limit, and linear range, so hs-CRP should also be tested in SLE patients.

Other influencing factors

The previous study[31] showed that the higher the SLEDAI, the greater the working memory impairment in SLE patients. We collected the data of SLEDAI for the first admission visit and found no significant difference between the two groups. In addition, there were also no statistically significant differences in indicators reflecting disease activity such as lupus nephritis and 24-hour urinary protein quantification, which suggest that CD is unrelated to disease activity in SLE patients, and cognitive function may be relatively stable with an insidious clinical symptom.

Besides, Katz et al.[32] found that obesity (OR = 14.8, 95%CI:1.4–151.0) and inactivity (OR = 9.4, 95% CI:1.7–52.8) were significantly and independently correlated with CD in multifactorial studies. In our study, the average BMI, levels of cholesterol, and triglyceride were all within the normal range, and most patients do not have obesity.

In addition, the previous study[33] suggested that CD was transient and reversible in SLE patients, and only about 4% of SLE patients were reported to have sustained CD within 5 years. Out of the 10 patients who had the history of NPSLE we assessed, 6 had normal scores on the MoCA scale. One of them was in a very poor state, diagnosed NPSLE more than a month ago, and could not cooperate with the scale at all, but after the disease was controlled, the one's cognitive function was undamaged. Thus it was considered that the cognitive function was reversible, which was consistent with the previous study.[34] But it still needs to be confirmed by further cohort studies.

The neurotoxicity of glucocorticoids has always been concerned across the world. McLaurin et al.[35] demonstrated that long-term use of prednisone was associated with decreased cognitive function in patients with SLE. And the continued use can aggravate the severity of SLE, which is caused by the neurotoxicity of glucocorticoids.[36] In our study, all patients were continuously treated with glucocorticoids or immunosuppressants to control the disease, but no correlation was found between drugs and SLE-related CD. The possible reasons are that patients have a different course of the disease, during which the dosage of drugs and other processes are complicated. Considering that patients are prone to have recall bias, only the current dosage and maximum dosage of glucocorticoids are collected, and the total amount is not discussed. And it should be noted that although RA has more cognitive impairment than controls, no correlation of this problem with cumulative glucocorticoid doses was found.[37] In the future, we will explore this issue deeply in SLE patients.

The elderly and low education levels are generally considered to be the risk factors of CD. Our study did not include elderly patients. We did find that the longer the time of education, the lower the risk of CD, which is consistent with the common understanding. None of the clinical manifestations of SLE patients showed any correlation with CD, so laterally it was confirmed that SLE related CD was a weak subclinical manifestation.

The limitation of this study is that this is a single-center study and lacks data on accumulated prednisone dosage. In conclusion, we indicate that the problem of SLE related CD should arise the attention of clinicians and patients in China. Serum anti-NMDAR antibodies can be used as a predictor for SLE related CD. Further large sample, multicenter, follow-up study should be conducted to dynamically monitor the changes in patients' cognition, laboratory indicators, and neuroimaging tests to better understand the relationship between BBB destruction, antibody titer, and patients' quality of life.[1]

Declaration of conflicting interests

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors received the grant from Guangdong Science and Technology Department (grant number: 2016A020215121.) for the study.

Ethical approval

This study was approved by the Research and Ethics Institutional Committee of Nanfang Hospital.

Guarantor

Xue-Biao Peng is the guarantor of this article.

Contributorship

The manuscript has been read and approved by all of the authors. Conceived and designed the experiments: Rui Yue, Ishwor Gurung, Xue-Biao Peng; performed the experiments: Rui Yue, Xin-Xin Long, Jia-Yi Xian; analyzed the data: Rui Yue, Ishwor Gurung; wrote the paper: Rui Yue, Ishwor Gurung.

Acknowledgements

We thank the Laboratory Department of Nanfang Hospital of Southern Medical University for laboratory information about autoantibodies. We also like to thank Dhirendra Paudel for the critical reading of the manuscript and technical help.

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