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Neuropsychiatric manifestations and magnetic resonance spectroscopy of the brain in systemic lupus erythematosus patients

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Abstract

Background Neuropsychiatric manifestations of lupus (NPSLE) are considered one of the major and most devastating lupus manifestations. The aim of this study was to assess the neuropsychiatric manifestations in systemic lupus erythematosus (SLE) patients and estimate the effectiveness of brain magnetic resonance spectroscopy (MRS) and anti-ribosomal P antibody test in early detection of NPSLE. This cross-sectional study was carried out on 50 SLE patients. Demographic, clinical, and therapeutic data were assessed. All patients were subjected to thorough rheumatological and neuropsychiatric evaluation. Serologic tests included antinuclear antibodies, anti-double-stranded DNA, and anti-ribosomal P protein antibodies. Radiologic evaluation included brain MRS.

Results The mean age was 26.9 ± 98.9 years; the median disease duration was 18 (0–108) months. Headache was the most common neurological symptom (40%). Depression was not detected in 29 patients (58%), mild in 15 patients (30%), and moderate in 6 patients (12%). Anti-ribosomal P antibody titer was significantly elevated in patients with active in comparison with those with inactive lupus disease ($p = 0.026$). Brain MRS showed a statistically significant reduction in N-acetylaspartate creatine ratio (NAA/Cr) among patients with active lupus disease ($p = 0.015$) with a statistically significant increase in choline creatine ratio (Cho/Cr) among patients with inactive lupus disease ($p = 0.049$). There was a statistically significant negative correlation between the level of NAA/Cr and anti-ribosomal P antibody titer among patients with active lupus disease ($p < 0.001$).

Conclusions Headache is the most common neurological manifestation among SLE patients. Anti-ribosomal P antibody titer is elevated in active SLE patients. The changes of NAA/Cr and Cho/Cr in brain MRS can be of help to differentiate between the active and inactive SLE.

Keywords Systemic lupus erythematosus, Neuropsychiatric lupus, Anti-ribosomal P antibodies, MRS

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Background

Systemic lupus erythematosus (SLE) is an autoimmune multisystem disease characterized by immune complex deposition that leads to the appearance of variable clinical manifestations [1]. It is usually presented in the middle age and affects females as nine times as males [2].

Mucocutaneous, renal, articular, hematologic, and serosal in addition to neuropsychiatric involvements are the major clinical features of SLE [3]. Neuropsychiatric manifestations of SLE (NPSLE) are considered one of the major and most devastating lupus manifestations. The reported prevalence of NPSLE events in SLE patients ranges from 11 to 81% [4]. It involves variable neurological syndromes including peripheral, autonomic, and central nervous systems, in addition to psychiatric syndromes [5]. Because of this variability in the clinical manifestations, the American College of Rheumatology research committee developed case definitions for 19 neuropsychiatric syndromes in SLE [6]. NPSLE can occur in the presence or absence of global disease activity [7].

The pathogenesis of NPSLE is still not well understood; however, cytokine-enhanced autoimmunity and complex brain-reactive autoantibodies are suggested to have a role in the pathogenesis [8]. No single test or radiological method is considered highly sensitive or specific for NPSLE. So, combined clinical, laboratory, and radiological procedures are needed to establish the diagnosis of NPSLE [9].

When it comes to the clinical evaluation of individuals who have NPSLE, the magnetic resonance imaging (MRI) of the brain is the method of choice [10]. However, MRI is not specific for NPSLE, and approximately half of the clinical manifestations occur in the early stages of the disease. There are no neuroradiological or immunological biomarkers that can predict the occurrence of such events in advance, so there is no way to antedate the occurrence of such events [11]. Therefore, magnetic resonance spectroscopy (MRS) could be an innovative neuroimaging method for the early detection of NS SLE.

This study aimed at assessing the neuropsychiatric manifestations in SLE patients. Furthermore, it also intended to estimate the effectiveness of brain magnetic resonance spectroscopy (MRS) in the early detection of NPSLE in comparison with the anti-ribosomal P antibody test and compare the brain MRS changes among active and inactive SLE cases.

Methods

Patients and study design

This was an observational analytical cross-sectional study. Patients were recruited from Rheumatology and Immunology Unit at Mansoura University Hospital, Egypt, between June 2018 and July 2019. All patients met the following inclusion criteria : (a) age $\geq$ 18 years and (b) classified as having SLE according to the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria [12]. Exclusion criteria included a history of chronic disease such as diabetes mellitus, hypertension, chronic renal failure, or any other associated organ failure. Those who had overlap syndrome with other autoimmune diseases were also excluded. The study protocol was approved by the Institutional Research Board of the Faculty of Medicine, Mansoura University (approval registration number: MD/17.04.81). The study was described to all patients, and an informed written consent was obtained from all of them before starting the study.

Sample size

Based on a previous study by Ainiala et al. [13], we hypothesized a 91% prevalence of NP manifestations among SLE patients. Sample size (n) was calculated by the following formula [14]:

$$n = \frac{z^2 \times P \times (1 - P)}{d^2}$$

A total sample size of 33 SLE patients achieves an 80% confidence level ($z = 1.282$) for an expected prevalence (P) of 0.83 and an acceptable margin of error (d) of ± 0.05. This sample size is sufficient to run statistical analysis to predict NP manifestations in SLE patients [15].

Demographic, clinical, and laboratory data

For the included patients, data regarding age, sex, residence, disease duration, and therapeutic history were recruited. A clinical examination was undertaken for all patients with emphasis on clinical manifestations of SLE. Laboratory data were also recorded with special consideration to complete blood count, urine analysis, C3 and C4 levels, and autoantibody profile including ANA and anti-dsDNA. The disease activity was calculated using SLEDAI [16] where a score value of 4 or less was considered low lupus disease activity state while a score value of more than 4 was considered moderate, high, or very high lupus activity [17].

Assessment of neuropsychiatric manifestations

All patients were neurologically examined and assessed for the level of consciousness, organic brain syndrome, seizures, cranial nerves, peripheral nerves, motor system, and autonomic nervous system. Also, all patients were assessed for any evidence of psychiatric disorders. Neurological and psychological evaluation was carried out by an experienced neurologist and psychiatrist. Additional laboratory tests and imaging scans confirm the preliminary diagnosis.

Hamilton Depression Rating Scale (HAM-D) [18] and Hamilton Anxiety Rating Scale (HARS) [19] were used to assess the level of depression and anxiety respectively in all participants.

The Mini-Mental State Examination (MMSE) test [20] was used for cognitive screening in this study, while Wechsler Memory Scale Partitions Logical Memory, Digits Forward, and Digits Backward was used for appraising major dimensions of memory function.

Measurement of anti-ribosomal P protein antibody

The sera of all participants were assayed for the anti-ribosomal P protein antibody level using ELISA assay. The antibody level below 20 units/ml was considered negative, from 20 to 39 units/ml weakly positive, from 40 to 80 units/ml moderately positive, and above 80 units/ml strongly positive.

Magnetic resonance spectroscopy protocol and data analysis

All MR examinations were performed on a 1.5-Tesla scanner (Ingenia, Philips) with a head circular polarization surface coil. Conventional MRI was done prior to MRS examination; parameters included T1-weighted sequence (TR/TE, 475/15 ms); T2-weighted sequence (TR/TE, 3607/100 ms); matrix size 80 × 80; slice thickness 3 mm; and inter-slice gap 1.8 mm.

H1 MRS was performed with a multi-voxel technique using a point-resolved spectroscopy sequence (PRESS) with the following parameters: repetition time (TR) of 1500 ms; intermediate echo time (TE) of 144; field of view, 16 cm; and slice thickness, 10 mm. For optimization of magnetic field homogeneity, suppression of outer volume fat and magnetic shimming were performed automatically for all patients at the beginning of the examination. Moreover, placement of within field-of-view saturation bands suppresses signals from osseous structures and CSF-containing structures adjacent to the tissue of interest to obtain satisfactory spectra. Acquisition of images was done at the basal ganglia level.

All spectroscopic data were transferred to a separate workstation for offline postprocessing using the machine software. The volume of interest (VOI) was determined by axial T2-weighted images; voxels were placed over the cortex of the posterior cingulate gyrus above the parieto-occipital sulcus. Within the defined VOI, separate 1 × 1 × 1 cm^3 voxels were placed.

The signal intensity of various metabolite peaks was evaluated in every voxel by using the integral of each peak as a measure of its intensity. The spectra were analyzed for the signal intensity of N-acetyl aspartate (NAA) at 2.02 ppm, choline (Cho) compounds at 3.2 ppm, creatine (Cr) at 3.02 ppm, and myo-inositol (mI) at 3.56 ppm. Metabolite ratios for N-acetylaspartate creatine ratio (NAA/Cr), choline creatine ratio (Cho/Cr), and mI/Cr were automatically calculated in the multiple voxels of interest.

Statistical analysis

The collected data were coded, processed, and analyzed using IBM SPSS for Windows v24 (IBM Corp., Armonk, NY). The distribution of continuous variables was examined for normality using the Shapiro–Wilk test. Data are expressed as the mean ± standard deviation if normally distributed or as the median, minimum, and maximum if not normally distributed. Qualitative data are presented as frequencies and relative percentages. The Mann–Whitney test and independent samples *t*-test were used to compare continuous variables. The chi-square test was used to assess the differences between qualitative variables. Receiver operating characteristic (ROC) curve analysis was done for anti-ribosomal P titer and MR spectroscopy metabolites to identify the cut points for activity in SLE. *p*-values of ≤ 0.05 were considered significant.

Results

The sample consisted of 50 SLE patients who fulfilled the inclusion criteria during the study period. The patients' characteristics are illustrated in Table 1. All of them were females with mean age of 26.98 years (*SD* 8.95). The median disease duration was 18 months. Cutaneous manifestations were the most predominant clinical feature among the study patients (52%), followed by hematological manifestations (50%) and then arthritis (40%), nephritis (38%), and serositis (16%), and vasculitis was the least (4%).

Regarding neuropsychiatric manifestations, headache was the most common neurological symptom (40%) as followed by psychosis (24%) and polyneuropathy, seizures, and acute confusional state, each of them 12%, and then, the least frequent was cerebrovascular accident (4%). Demyelinating syndrome, myelopathy, movement disorders, aseptic meningitis, autonomic neuropathy, and myasthenia gravis were not detected in our study patients as shown in Table 2.

According to HAM-D scores, depression was not detected in 29 patients (58%), mild in 15 patients (30%), and moderate in 6 patients (12%). HARS score interpretation revealed no evidence of anxiety in 25 patients (50%), mild in 13 patients (26%), and moderate in 12 patients (24%) as shown in Table 2.

Using the SLEDAI score, 20 patients (40%) showed low disease activity (group 1), while 30 patients (60%) showed moderate, high, or very high disease activity (group 2). Table 3 shows the comparison between the 2 groups. There was no significant difference between the 2 groups

Table 1 Demographic, clinical, laboratory, treatment characteristics in the study of SLE patients ($n = 50$)

Characteristic	SLE patients ($n = 50$)
Demographic and clinical characteristics	
Age (years), M ± SD	26.98 ± 8.95
Sex, *n* (%)	
Female	50 (100)
Residence, *n* (%)	
Urban	26 (52)
Rural	24 (48)
SLE disease duration (months), median (min–max)	18 (0–108)
Lupus-related manifestations, *n* (%)	
Cutaneous manifestations	26 (52)
Vasculitis	2 (4)
Nephritis	19 (38)
Arthritis	20 (40)
Serositis	8 (16)
Hematological abnormalities	25 (50)
Laboratory characteristics, *n* (%)	
Thrombocytopenia	5 (10)
Leucopenia	5 (10)
Urinary casts	5 (10)
Hematuria	14 (28)
Proteinuria	22 (44)
Pyuria	19 (38)
Serological markers for SLE	
Positive ANA, *n* (%)	50 (100)
Positive anti-dsDNA, *n* (%)	16 (32)
SLEDAI score, median (min–max)	14 (1–20)
Immunosuppressive medications used for treatment, *n* (%)	
Steroids	50 (100)
IV pulse methylprednisolone high dose	15 (30)
Moderate dose	7 (14)
Low dose	18 (36)
Hydroxychloroquine	10 (20)
Azathioprine	28 (56)
Mycophenolate mofetil	35 (70)
Cyclophosphamide	10 (20)

ANA antinuclear antibodies, *anti-dsDNA* anti-double-stranded DNA, *SLE* systemic lupus erythematosus, *SLEDAI* systemic lupus erythematosus disease activity index

regarding age, depression, anxiety, memory, and cognition scores. However, anti-ribosomal P antibody titer was significantly elevated in group 2 in comparison with group 1 ($p = 0.026$).

Brain MR spectroscopy results showed a statistically significant reduction in NAA/Cr among group 2 patients in comparison with group 1 ($p = 0.015$) with a statistically significant increase in Cho/Cr among patients in group 1 when compared with those in group 2 ($p = 0.049$).

There was a highly statistically significant negative correlation between the level of NAA/Cr and anti-ribosomal P antibody titer among group 2 ($SLEDAI > 4$) ($p < 0.001$) as shown in Table 3. A correlation between MR spectroscopic measurements and anti-ribosomal P antibody titer is shown in Table 4.

The validity of anti-ribosomal P antibody and MR spectroscopic measurements in posterior cingulate gyrus in differentiating between active and inactive SLE patients is shown in Table 5.

Table 2 Neuropsychiatric manifestations, anti-ribosomal P protein level, and brain MRS findings in the study SLE patients ($n = 50$)

Characteristic	SLE patients ($n = 50$)
Neurological manifestations, *n* (%)	
Headache	20 (40)
Psychosis	12 (24)
Seizures	6 (12)
Polyneuropathy	6 (12)
Acute confusional state	6 (12)
Cerebrovascular accidents	2 (4)
Myelopathy	0
Movement disorders	0
Aseptic meningitis	0
Demyelinating syndrome	0
Autonomic neuropathy	0
Myasthenia gravis	0
Psychiatric scores	
HAM-D, *n* (%)	
Negative	29 (58)
Mild	15 (30)
Moderate	6 (12)
HARS	
Negative	25 (50)
Mild to moderate	13 (26)
Moderate to severe	12 (24)
MMSE, M ± SD	28.98 ± 1.38
W. logical memory, M ± SD	14.48 ± 5.27
W. digits forward, M ± SD	4.78 ± 1.58
W. digits backward, median (min–max)	3 (0–5)
Anti-ribosomal P protein antibody (units/ml), median (min–max)	13 (2.5–88.7)
MRS measurements in the posterior cingulate gyrus, M ± SD	
NAA/Cr	1.61 ± 0.23
Cho/Cr	0.97 ± 0.19
mI/Cr	0.53 ± 0.10

HAM-D Hamilton Depression Rating Scale, *HARS* Hamilton Anxiety Rating Scale, *MMSE* Mini-Mental State Exam, *Cho* choline compound, *Cr* creatine and phosphocreatine, *mI* myo-inositol, *NAA* N-acetylaspartate

ROC curves were developed to identify the threshold values of NAA/Cr and mI/Cr, Cho/Cr, and anti-ribosomal P that differentiate SLE patients with low disease activity from those with moderate to severe disease activity as shown in Fig. 1. Brain MR spectroscopy in SLE patients with inactive disease and active disease is demonstrated in Fig. 2.

Discussion

In this study, headache was the most common neuropsychiatric manifestation in SLE patients, though cognitive function and mood disorders were not affected by the lupus disease activity. Anti-ribosomal P antibody titer was elevated in active NPSLE patients. Moreover, brain MRS results showed a statistically significant reduction in NAA/Cr ratio and elevation of Cho/Cr in active SLE patients with a significant association between Cho/Cr level and lupus disease activity. Taken together, the anti-ribosomal P antibody level in addition to brain MRS with changes of NAA/Cr and Cho/Cr can help in early detection of NPSLE and differentiation between patients with active and inactive SLE.

Headache was the most common neuropsychiatric manifestation in the current study, reported by 40% of patients, followed by psychosis, seizures, polyneuropathy, and acute confusional state, and then lastly, cerebrovascular accidents. In a meta-analysis of studies assessing the prevalence of NPSLE manifestations, headache was present in 56% of SLE patients, denoting that headache was the predominant NPSLE symptoms [21]. However, the order of frequency of each NPSLE manifestation was not agreed upon in other studies; specifically, in one study, the rate of headache in SLE patients was not dissimilar to that reported in the normal population [22].

Demyelinating syndrome, myelopathy, movement disorders, aseptic meningitis, autonomic neuropathy, and myasthenia gravis are very rare manifestations of NPSLE [23] and were not detected in the current study because the sample size was relatively small.

Depression is considered as the most common mood disorder in NPLSE accounting for up to 65% of SLE patients [24]. In this study, depression was found to affect 42% of patients, a finding that agrees with that of Bachen et al. [24], although Tay and colleagues [25] reported depression in only 15.5% of SLE patients. This disagreement could be attributable to the difference in the ethnical background; the former study was conducted on the French population, while the latter was conducted on the Singaporean population.

On the other hand, anxiety is common in SLE patients and has been shown to afflict up to 40% of patients [26], a finding which accords to that of the current study. Moreover, and similar to what has been discussed with depression, anxiety did not seem to be enhanced by disease activity, both in the present study and previous reports [27, 28]. However, this is in contrast to the findings reported in another study [29] in which anxiety was aggravated by the global disease activity.

In the present study, anti-ribosomal P antibody titers were elevated in a statistically significant value in active SLE patients, and again, it was not associated with any specific neurological manifestations. In accordance with this, in a Polish study conducted by Olesinska and coworkers, anti-ribosomal P antibody was associated with disease activity [30]. On the other hand, other

Table 3 Comparison between patients with inactive versus patients with active lupus disease regarding clinical, serological, and brain MRS measurements in the posterior cingulate gyrus

Characteristic	SLEDAI score		Test of significance	*p*
	Group 1 (low disease activity) ($n = 20$)	Group 2 (moderate to very high disease activity) ($n = 30$)		
Demographic and clinical characteristics				
Age (years), M ± SD	26.15 ± 8.86	27.53 ± 9.12	$t = -0.531$	0.372
Residence, *n* (%)				
Urban	9 (45)	17 (57)	$\chi^2 = 0.654$	0.419
Rural	11 (55)	13 (57)		
SLEDAI score	1.90 ± 0.72	16.0 ± 2.28		< 0.001*
Neuropsychiatric manifestations, *n* (%)				
Headache	7 (35)	13 (43.3)	$\chi^2 = 0.437$	0.56
Psychosis	6 (30)	6 (20)	$\chi^2 = 0.658$	0.42
Seizures	3 (15)	3 (10)	$\chi^2 = 284$	0.67
Polyneuropathy	4 (20)	2 (6.7)	$\chi^2 = 2.02$	0.2
Acute confusional state	0 (0)	6 (12)	$\chi^2 = 4.545$	0.03*
Cerebrovascular accidents	0 (0)	2 (6.7)	$\chi^2 = 1.389$	0.24
Psychiatric scores				
HAM-D, *n* (%)				
Negative	11 (55)	18 (60)	$\chi^2 = 2.524$	0.28
Mild	8 (40)	7 (23.3)		
Moderate	1 (5)	5 (16.7)		
HARS, *n* (%)				
Negative	9 (45)	17 (56.6)	$\chi^2 = 1.427$	0.49
Mild to moderate	7 (35)	5 (16.7)		
Moderate to severe	4 (20)	8 (26.7)		
MMSE, M ± SD	29.35 ± 0.88	28.73 ± 1.59	$t = 1.574$	0.12
W. logical memory, M ± SD	15.65 ± 4	13.70 ± 5.91	$t = 1.290$	0.20
W. digits forward, M ± SD	4.55 ± 1.82	4.93 ± 1.41	$t = -0.837$	0.41
W. digits backward, M ± SD	2.60 ± 1.05	2.83 ± 1.42	$t = -0.630$	0.67
Total Wechsler Memory Scale, M ± SD	22.80 ± 5.11	21.47 ± 7.26	$t = 0.831$	0.48
Cognition as whole, M ± SD	52.15 ± 5.38	50.20 ± 8.09	$t = 0.521$	0.35
Anti-ribosomal P protein antibody (units/ml), median (min–max)	8.5 (2.5–46.3)	17.55 (2.70–88.7)	$MWT = -1.891$	0.026*
MRS measurements in the posterior cingulate gyrus, M ± SD				
NAA/Cr	1.71 ± 0.2	1.55 ± 0.24	$t = 2.531$	0.015*
Cho/Cr	0.91 ± 0.19	1.02 ± 0.18	$t = -2.022$	0.049*
mI/Cr	0.54 ± 0.1	0.53 ± 0.1	$t = 0.632$	0.53

MWT Mann–Whitney test. *Cho* choline compound, *Cr* creatine and phosphocreatine, *HAM-D* Hamilton Depression Rating Scale, *HARS* Hamilton Anxiety Rating Scale, *mI* myo-inositol, *MMSE* Mini-Mental State Exam, *NAA* N-acetylaspartate, *SLEDAI* systemic lupus erythematosus disease activity index

* $p \leq 0.05$, χ^2 chi-square, *t* independent sample *t*-test

studies [31, 32] failed to find such an association. In addition, the presence of anti-ribosomal P antibody did not predict the occurrence of neuropsychiatric manifestations [32, 33]. The variations in these results could be perceived in the light of the known controversy on the possible pathogenic and clinical role of anti-ribosomal P antibody in NPSLE [34].

In the present study, brain MRS was selected to investigate cerebro-neuronal damage that is possibly related to SLE. Brain MRS is believed to be capable of providing information about the chemical profile of neuronal tissue, making use of some relevant neurometabolites as N-acetylaspartate (NAA), which has been reported to be higher in concentration in healthy neurons and axons;

Table 4 Correlation between MR spectroscopic measurements and anti-ribosomal P antibody titer in group 2 patients (*SLEDAI* > 4) ($n = 30$)

Variable	Anti-ribosomal P antibody titer	
	rs	*P*
NAA/Cr	−0.579	0.001*
Cho Cr	−0.173	0.361
mI/Cr	0.268	0.25

Cho choline compound, *Cr* creatine and phosphocreatine, *mI* myo-inositol, *NAA* N-acetylaspartate

* $p \leq 0.05$

significantly reduced while Cho/Cr was statistically significantly increased among the active compared to the inactive SLE cases.

Prediction and/or early identification of NPSLE activity may be pivotal for the investigation of early management plans which could be rewarding for improving disease outcome. Interestingly, the present study showed a highly statistically significant negative correlation between the level of NAA/Cr and anti-ribosomal P antibody titer among the active SLE cases, while this relation was not significant in the inactive cases, findings that reinforce the application of anti-ribosomal P antibody and brain MRS, relying on NAA/Cr, in assessment and monitoring of NPSLE disease activity.

Table 5 Validity of anti-ribosomal P antibody and MR spectroscopic measurements in posterior cingulate gyrus in differentiating between active and inactive SLE patients

	AUC	(95% *CI*)	Cutoff point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Anti-ribosomal P antibody	0.687	(0.537–0.83)	≥ 9.30	76.7	55	74.2	63.2	70
MR spectroscopic measurements								
NAA/Cr	0.71	(0.57–0.85)	≤ 1.5750	66.7	75	80	60	70
Cho/Cr	0.677	(0.53–0.83)	≥ 1.02	66.7	60	71.4	54.5	64
mI/Cr	0.55	(0.38–0.71)	≤ 0.565	60	45	62.1	42.9	70

AUC area under the curve, *Cho* choline compound, *Cr* creatine and phosphocreatine, *mI* myo-inositol, *NAA* N-acetylaspartate

thus, it may be considered as a valid marker of neuronal viability and axonal integrity. Similarly, choline (Cho) is another neurometabolite which can act as a marker of cell membrane turnover, synthesis, and degradation, while creatine (Cr) is the most constant metabolite and thus is used for ratio calculation [35]. In addition, myo-inositol (mI) is a neurometabolite that is known to be a good indicator of astrocyte integrity and regulation of brain osmosis, and its increase can reflect astrogliosis as well as neuronal and axonal damage; so, it may be considered as a marker of poor prognosis [36].

It was reported that NAA and NAA/Cr are reduced, while choline is increased in active NPSLE, changes that tended to normalize after activity control, reflecting a transitory axonal dysfunction in NPSLE. Moreover, the increase in choline was apparent in brain MRS before the occurrence of the neurologic manifestations; so, this was suggested to predict future cerebral involvement in SLE [37]. In addition, in a histopathological study of NPSLE, choline value was also shown to be elevated in association with active myelin breakdown accompanying gliosis, vasculopathy, and edema [38].

In harmony with previous data, brain MRS study in the present work revealed that NAA/Cr was statistically

On trying to differentiate between active and inactive SLE, the current study showed that the NAA/Cr level of brain MRS is valued with a higher area under the receiver observed curve compared to other studied allegedly determinants for SLE activity, viz., anti-ribosomal P antibody, choline/creat ratio, and mI/creat ratio. On the other hand, the variables statistically significantly associated with SLE activity, namely NAA/Cr, anti-ribosomal P antibody titer, and Cho/Cr, were entered in a multivariate logistic regression model for prediction of active SLE. Cho/Cr value proved to be the most strongly statistically significantly predictive of SLE disease activity, dismissing the other variables from the model, albeit published studies comparing between anti-ribosomal P antibody titer and brain MRS changes in active and inactive SLE are scarce and this issue needs further research.

There are few limitations to the present study. First, this current work adopted a cross-sectional design which fails to detect disease progression and the effect of therapy. Second, the number of studied cases was relatively small. Further studies based on a larger number of cases would be more decisive. Third, the MRS data were not correlated with the clinical findings. Finally, the unique

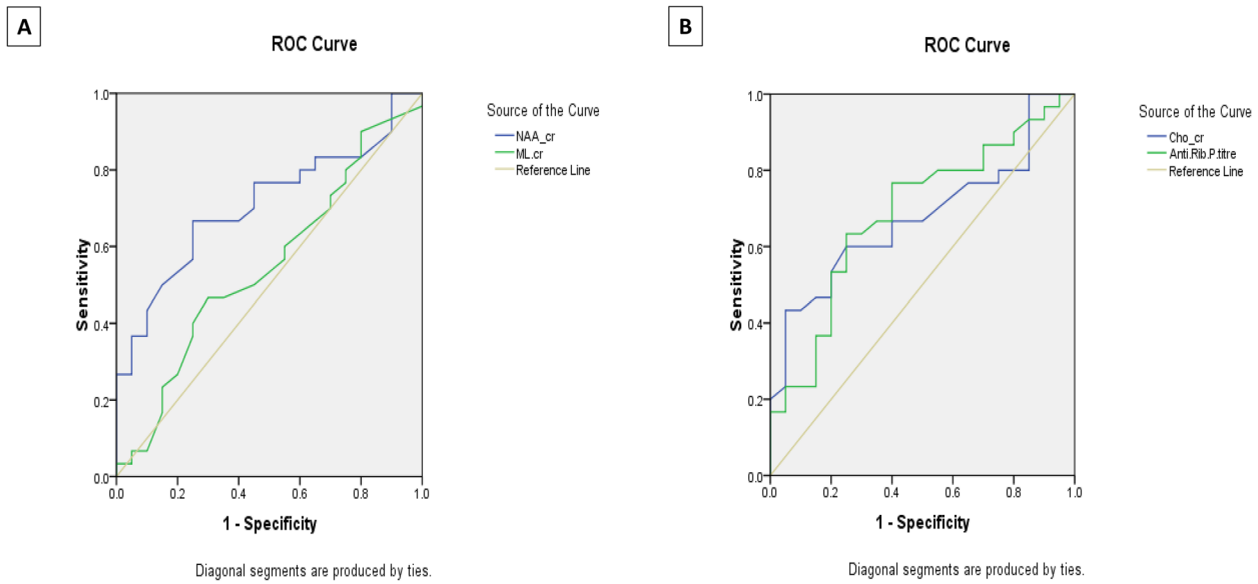

Fig. 1 **A** Receiver operating characteristic (ROC) curve for NAA/Cr and mI/Cr for differentiating active and inactive SLE. **B** ROC curve for Cho/Cr and anti-ribosomal P titer for differentiating active and inactive SLE ($n = 50$)

Fig. 2 Brain MR spectroscopy in SLE patients with **A** inactive disease and **B** active disease

ethnical background of Egyptian patients which is a mix of different Caucasian and African sources does not allow for comparison with other studies base on a monoethnic population.

Conclusions

Brain MRS is an advanced imaging technique that is considered promising in this respect and has been documented in the present study to add to the diagnosis of NPSLE and its activity. Particularly, more specific in this regard is the increase of choline/creatine peak by brain MRS, which was the strongest predictor of activity compared to the other neurometabolites by the same technique, as well as the anti-ribosomal P antibody serum titers. Thus, the present research suggests appropriate wider utilization of brain MRS during the care of SLE patients.

Abbreviations

Cho/Cr	Choline creatine ratio
HAM-D	Hamilton Depression Rating Scale
HARS	Hamilton Anxiety Rating Scale
MMSE	Mini-Mental State Examination
MRS	Magnetic resonance spectroscopy
NAA/Cr	N-Acetylaspartate creatine ratio

NPSLE	Neuropsychiatric manifestations of systemic lupus erythematosus
PRESS	Point-resolved spectroscopy sequence
SLE	Systemic lupus erythematosus
TR	Repetition time
VOI	The volume of interest

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Authors' contributions
Conceptualization, DAS, KMF, and ME. Investigation, all authors. Data curation and formal analysis, NAS, ME, and EM. Writing—original draft, AAA and ST. Writing—review and editing, all authors. The authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article or are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was performed in accordance with the Declaration of Helsinki. It was approved by the Institutional Research Board of the Faculty of Medicine, Mansoura University (approval number: MD/17.04.81). The study was explained to all participants, and informed written consent was obtained from all of them before starting the study. No parts of the final version of the manuscript contain copied parts and all co-authors take full responsibility for the integrity of the published article.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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