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Original Article

Event-related potential (P300) abnormalities and linked autoantibodies as a marker of early Cognitive dysfunction in patientswith Systemic Lupus Erythematous a case - control study

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Abstract:

Background: SLE patients frequently have primary central nervous system involvement. Cognitive changes, seizures, psychosis, and headache are a few of the symptoms. P300 is an electrical marker of disrupted CNS that is utilized to identify cognitive dysfunction even at the subclinical stage. The Montreal Cognitive Assessment Questionnaire (MoCA) has been used to detect moderate cognitive impairment.

Objective: Our study aims to assess and to detect cognitive dysfunction early in SLE (Neuropsychatric Systemic Lupus Erythematosus (NPSLE) or non-NPSLE) patients with P300 latency and MoCA. And to determine the relation of different SLE auto-antibodies and impaired P300 hence as a marker for cognitive dysfunction.

Results: Our study included 60 (57 female and 3 male) adult SLE patients with a mean age of 30 years old and 30 participants (26 female and 4 males) as a control group with a mean age of 34 Years. Regardless of whether there are evident or hidden CNS abnormalities, our current investigation demonstrated that ERP abnormalities are present in SLE patients. All SLE patients had significantly longer P300 delay with lower MoCA scores, indicating that P300 and MoCA are likely connected. Numerous autoantibodies were linked to P300 abnormalities.

Conclusion: EP and ERP are electrophysiological indicators of abnormal CNS activity, even in the preclinical state. P300 can be thought of as a marker for early CNS impairment in SLE. Numerous autoantibodies were linked to P300 aberrations and may be used as a marker for the onset of cognitive impairment.

Key points: Cognitive impairment are one of CNS disturbance in patients with SLE.

Keywords: systemic lupus erythematosus, event-related evoked potentials, Montreal cognitive assessment.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease with a wide range of clinical signs, a protracted illness, and an uncertain prognosis [(1)] . SLE has several causes, including complicated genetic factors, medicines, and environmental variables that may exacerbate the disorder [(2)].

The female-to-male ratio is 9:1, and the peak age of onset for young women is between their late teens and early 40s. The condition may be more severe in patients of ethnic groups other than Caucasians, such as those of African or Asian heritage [(3)].

The diagnosis of SLE depends on the SLE Collaborating Clinics Criteria (SLICC) [(2)]. In 2012, SLICC proposed revised classification criteria that were released to improve upon the 1997 American College of Rheumatology (ACR) classification criteria [(4)]. Systemic lupus erythematosus disease activity index (SLEDAI) measures SLE activity [(5)].

The nervous system is one of the major organs affected in patients with SLE [(6)]. Identifying and treating patients with Neuropsychatric Systemic Lupus Erythematosus (NPSLE) can be difficult for clinicians due to its highly variable presentation. CNS manifestations of SLE can range from acute confusional states, psychosis, seizure disorders, and stroke, to subtle cognitive dysfunction, which affects up to 50% of patients with SLE (even those with mild disease and no overt NPSLE manifestations) [(7)].

The true prevalence of NPSLE is unknown [(8)]. Numerous pathogenic mechanisms of NPSLE, including thrombosis, autoantibodies, cytokines, and cell-mediated inflammation, are most likely implicated [(9)]. To be more precise, in some cases, short- and long-term memory processing and verbal and visual-spatial information processing are affected. Attention may be also significantly affected, in SLE that presents with neuropsychiatric manifestation [(10)].

Nevertheless, it is tentatively predicted that CNS illness affects more than 20% of people with SLE, even once modest neuropsychiatric symptoms are ruled out. NPSLE is the second leading cause of death in the SLE community, behind lupus nephritis. It is also a major cause of morbidity in this group [(11)].

Cognitive dysfunction (CD) is a significant problem in SLE, reported to affect up to 90% of patients, the cause is unclear [(12)]. Impairment of cognition may be manifested by declining performance and subtle difficulties with working memory and concentration tasks [(13)].

A hallmark of SLE is the formation of autoantibodies, several of which are implicated in NPSLE manifestations [(14)]. Multiple autoantibodies are produced, which is a defining feature of SLE. Antinuclear antibody (ANA), which is detected in more than 95% of individuals with SLE, is the most prevalent autoantibody. Given that specific autoantibodies correlate with illness characteristics, it is appropriate to check for specific autoantibodies in the presence of an ANA, particularly those against double-stranded DNA (dsDNA) and extractable nuclear antigens (ENAs) [(15)].

It is thought that a significant portion of the autoantibodies found in NPSLE patients has a role in the etiology of the illness. Of these, autoantibody-mediated thrombosis (autoantibody-mediated thrombosis) is thought to be directly (though not exclusively) linked to focal NPSLE via aPL antibodies; other antibodies, like ant ribosomal P protein and anti-NMDAR antibodies, are thought to target specific brain parenchymal structures and may account for diffuse NPSLE presentations [(16)].

Patients with aPL antibody positivity have a higher risk of stroke and transient ischemic attack because the CNS is more prone to thrombus formation than most other organs [(17)]. Furthermore, an additional risk factor for cerebrovascular ischemia is atherosclerosis, which is accelerated by aPL antibodies. APL antibody-positive people have an approximately eight-fold increased risk of stroke compared to aPL antibody-negative people under the age of fifty [(18)].

The Montreal Cognitive Assessment Questionnaire (MoCA) is a one-page performance-based screening test that has been validated to identify mild cognitive impairment It has also been successfully utilized in several diseases including Parkinson's disease, Huntington's disease, cerebrovascular disease, and substance abuse disorders, and in SLE as well [(7)].

Neurophysiological abnormalities are fairly common in SLE patients whether symptomatic or asymptomatic [19]. The use of such tests (evoked potentials) favors a true incidence of nervous system involvement, and more accurate diagnosis, and may lead to better clinical care before the development of the debilitating central nervous system (CNS) and peripheral nervous system (PNS) changes [11].

Evoked potentials (EP) are electrophysiological markers of disturbed CNS, even in the subclinical stage [20], they detect functional dysfunction such as slow conduction in various neural pathways [21].

One of them is Event-related potential (P300), The P300 or P3 are the most commonly used long-latency auditory evoked potentials (LLAEP) in clinical practice; they are used for investigating cognition and attention [22]. An ERP element that is evoked during the decision-making process is the P300 (P3) wave. Since its existence is linked to an individual's response to a stimulus rather than the physical characteristics of the stimulus, it is regarded as an endogenous potential [12]. More specifically, the P300 is thought to reflect processes involved in stimulus evaluation or categorization [23].

Aim of this work:

we aimed in this study to assess and early detect cognitive dysfunction in SLE patients with or without manifest neuropsychological symptoms by measuring P300 and MoCA, and to assess the relationship between SLE activity and P300 latency. In addition to determining the relationship of different auto-antibodies and impaired P300 latency which may be used as a marker for the onset of cognitive impairment.

Patient and Methods:

This study is a Case-Control study.

The data for 60 adult SLE patients and 30 corresponding volunteers was collected in the

Rheumatology Department, Sohag University Hospital between November 2020 and July 2021.

Inclusion criteria:

1. Patients diagnosed as SLE according to SLICC 2012 .
2. Age (17-67) years

Exclusion criteria:

1. Patients with concomitant systemic diseases such as, chronic obstructive lung disease, coronary artery disease, cancer, thyroid function disorder, hematological disorders, acute or chronic liver and renal diseases
2. Other autoimmune disease including rheumatoid arthritis, scleroderma, mixed connective tissue disease and polymyositis.
3. Patients with other causes of cognitive impairment (e.g. mental retardation, brain atrophy).

The patient population were compared to 30 age - and sex matched volunteer persons as a control group with no history of collagen or systemic,or neurological deficits used to show if there any difference between P300 in normal population and All-SLE patients.

Patients' assessment:

1. All cases were underwent neurological and psychological assessment and diagnosis by well-trained neurologist and psychiatrist.
   The 2012 (SLICC) classification criteria for SLE were used to determine the patients' diagnoses ANA test was measured using the immunofluorescence approach (indirect immunofluorescent) (IIF) on HEp-2 cells,The higher the titer, the more likely the result is a “true positive” result, meaning you have significant ANAs and an autoimmune disease.
   For example, for a ratio of 1:40 or 1:80, the possibility of an autoimmune disorder is considered low. A ratio of 1:640 or greater indicates a high possibility of autoimmune disorder.

2. ANA profile for the 19 most prevalent autoantibodies determined by immunoblot: such as those against dsDNA, nucleosomes, anti-Smith, histone, SSA, etc. The disease activity in the patients was evaluated utilising the (SLEDAI) [2, 4].

3. Event-related potentials (ERPs) were measured using the "odd-ball" stimulation paradigm (Neuropack X1- MEB2300, Nihon KohdenCo., Japan). ERPs were captured utilizing the international 10-20 system using Ag/AgCl electrodes

at the frontal zone Fz, central zone Cz, and parietal zone Pz sites. The reference electrodes were connected to earlobe electrodes, and the recording electrodes were positioned at Fz, Cz, and Pz. The EEG signals were amplified and band passed (0.01-40 Hz) while electrode impedance was maintained below 5 k. In a serene space with low lighting, the volunteers underwent testing while seated in a comfy chair with a neck support.

Each subject received 20 ms of bilateral, 80 dB ear stimulation using headphones. The goal stimuli were 2000 Hz pure tone bursts, while the standard stimuli were 1000 Hz pure tone bursts. Variable time intervals between 1 and 2 s were used to give the inter-stimulus intervals. Each sound category's probability was 84.62% for standard stimuli and 15.38% for target stimuli. Random presentations of the two sound kinds were made. When the target stimulus was shown, the individuals were instructed to hit a button as soon as they could with their right thumb.

For each participant in the research, event-related potentials were captured at the same times of day (between 9 and 12 AM) .Patients and controls were instructed to unwind and focus on a specific spot on the front wall to reduce visual artifacts and boost attention during recording.. P300 waves have been identified.

We measured the peak-to-peak amplitudes of P300. For each example, we calculated the P300 delay at Cz, Pz and Fz. The one-page, performance-based Montreal Cognitive Assessment Questionnaire MoCA is effective in detecting mild cognitive impairment [24, 25].

Statistical analysis:

The statistical data analysis was performed using the IBM-SPSS, version 24; IBM-Chicago, USA. Using the Kolmogorov-Smirnov test, the normality of the data distribution was found.

Data was presented as percentages and numbers for qualitative data. For quantitative data that was regularly distributed, the mean and standard deviation were utilised as descriptive values, and for non-parametric data, the median and range. When non-parametric data are present, the Mann-Whitney test is used in place of the Student t-test to compare medians rather than the means between two groups.

When comparing two quantitative variables, the Pearson correlation test was employed, and the Spearman correlation test was substituted if the data were not parametric.

- r <0.2 ➔ negligible correlation
- r 0.2-0.4 ➔ weak correlation
- r 0.4-0.7 ➔ moderate correlation
- r 0.7-1 ➔ strong correlation
- r positive ➔ positive correlation
- r negative ➔ negative correlation

Mann Whitney test was used to Relation between P300 latency and different antibodies among neuropsychatric SLE cases

For all these tests, the level of significance (P-value) can be explained as:

*No significance P >0.05

*Significance P < 0.05

*High significance P < 0.001.

Results:

Our study included 60 adult SLE patients and 30 as a control group. The demographic, and clinical findings of the SLE patients and SLEDAI score are shown in (table 1).

Table 1. shows demographic and clinical data and the SLEDAI Score of the study group

Age(years)	-SLE group mean=30 (22-54) -Control group mean= 34 (21-51)
Sex (Female to male ratio)	-SLE group 57-3(95%-5%) -control group26-4 (86.6%-13.3%)
Disease duration (years)	Mean ± SD (5.1 ± 3.57)
Clinical manifestations	(Number of cases (Percent)
Constitutional	28 (46.4%)
-Mucocutaneous	43 (71.6%)
-Musculoskeletal	31 (51.7%)
-Pulmonary	15(25%)
-Cardiovascular	12(20%)
-Hematological	27(45%)
-Lupus nephritis	29(48.3%)
-Gastrointestinal	17(28.3%)
SLE-DAI score (frequency)	
-Mild	7
- Moderate	19
-Severe	26
-High severe	8

Mucocutaneous affection was the commonest followed by musculoskeletal one. Overt neurological manifestations of SLE patients were observed in 30 patients(50%) discussed in (table 2). Medication data are shown in (table 3).

Table 2. Manifestations of NPSLE patients

SLE without neuropsychiatric manifestations	30(50%)
SLE with neuropsychiatric manifestations	30(50%)
-Psychosis	6 (20%)
-Stroke	5(16-.6%)
-Seizures	8 (26.7%)
-Myelitis	1(3.3%)
-Peripheral neuropathy	2 (6.7%)
-Acute confusional state	5 (16.6%)
-Optic neuropathy	3 (10%)

Table 3. DMARD therapy used by the study group

Disease-modifying therapy	Number of cases
Hydroxychloroquine	59
Azathioprine	49
Cyclophosphamide	45
Mycophenolate Mofetil	11
Corticosteroid therapy	
Oral dose	10(5-40)
I.V dose (cumulative doses number)	1(0-6)

Significant positive correlation between P300 latencies in all SLE patients and SLEDAI score (r=0.531) at p-value < 0.0001. No correlation was found between P300 latencies in all SLE patients and disease duration (r=0.152) (p-value 0.08).A negative non-significant correlation between steroid dose and p300 latency (r=-0.04) (p-value 0.7).

There was a highly significant negative correlation between MOCA and p300 latency in all SLE patients (r = -0.73) (p-value 0.0001). There was a significant negative correlation between MoCA and SLEDAI scores in SLE patients (r= -0.44) (p-value 0.01). There was a non-significant negative correlation between MOCA and steroid dose in all SLE cases (r=-0.05) (p-value 0.7).

As regards the results of SLE autoantibodies only anti-double-stranded DNA was found to be a associated with a prolonged P300 latency in SLE patients with or without manifest neuropsychiatric manifestations (p values 0.001). . positive anti double strand DNA cases among SLE cases have significant higher median of P300 latency level in comparison to negative cases (424.64 ± 88.66 and 359.63 ± 7.42). However, there is insignificant difference relation between P 300 latency with anti-ribosomal-p, anti-nucleosome antibody and anti-RNP among SLE cases(table 4).

Anti-APS antibodies weren't found to be a predictor for abnormalities of P300 in SLE patients with a p-value of 0.9

Regarding P300 latency results, we found that P300 latencies in all SLE patients with or without NPSLE manifestations were significantly prolonged compared to the control group as shown in (table 5). MoCA scores were significantly higher in the control group than in SLE patients with a non-significant difference between MoCA scores of NPSLE cases and Non-NPSLE patients as shown in (table 5). There was a significant difference in MOCA scores between Non-NPSLE patients and control groups and was highly significantly lower in the NPSLE group than in the control group (table 5).

Table (4) Relation between P300 latency and different antibodies among SLE (NPSLE and non-NPSLE)cases(60 cases)

P300 latency	Positive group	Negative group	P-value
Anti-ribosomal-p			
Mean ± SD	426.53 ± 104.98	388.07 ± 42.13	0.14
Median (IQR)	374 (358-474)	372 (370-381)	
Anti-nucleosome antibody			
Mean ± SD	398.81 ± 56.59	417 ± 103.68	0.8
Median (IQR)	374 (361.25-447.75)	372 (367-464.5)	
Anti-double strand DNA			
Mean ± SD	424.64 ± 88.66	359.63 ± 7.42	< 0.001
Median (IQR)	377.5 (372-472.5)	358 (355-367)	
Anti-RNP			
Mean ± SD	425.21 ± 94.93	376.36 ± 33.77	0.1
Median (IQR)	374 (370-472)	372 (358-374)	

Table 5. Results of P300 latencies and MoCA scores in SLE(NPSLE &non-NPSLE) patients and control group.

	All SLE	Control	NPSLE	Non-NPSLE
P300 Latencies in ms at Cz point	Median(Range) 374 (299-543)	Median(Range) 299(265-335)	Median(Range) 373(351-536)	Median(Range) 377(299-543)
	P value <0.0001		P value 0.824	
P300 latencies in ms at fz point	Median(Range) 375(300-540)	Median(Range) 299(260-345)	Median(Range) 375(352-536)	Median(Range) 379(300-540)
	P value<0.0001		P value0.6	
P300 latencies in ms at pz point	Median(Range) 377(298-543)	Median(Range) 300(269-344)	Median(Range) 377(352-535)	Median(Range) 377(298-543)
	P value<0.0001		P value0.5	
P300 amp at Cz	Median(Range) 6.8(1.8-19.9)	Median(Range) 6.3(3.5-20.3)	Median(Range) 9.1(2.6-16.2)	Median(Range) 6.4(1.8-19.9)
	P value0.99		P value0.16	
P300 amp at fz	Median(Range) 6.7(2.3-19)	Median(Range) 5.4(2.4-21.2)	Median(Range) 9.9(3.1-13.2)	Median(Range) 5.1(2.3-19)
	P value0.61		P value0.19	
P300 amp at Pz	Median(Range) 5.3(1.5-14.3)	Median(Range) 6.4(3.6-21.8)	Median(Range) 5.9(2.7-14.3)	Median(Range) 5.2(1.5-13.66)
	P value0.055		P value 0.3	
MoCA score	Median(Rang) 24(17-30)	Median(Rang) 28(27-30)	Median(Rang) 23.5(18-30)	Median(Range) 24.5(17-30)
	P value <0.001		P value0.733	

Discussion

In our study we found that the range of SLE's symptoms in the nervous system is enormous, and both the central and peripheral nervous systems may be affected [26]. It has been discovered that SLE includes mild subclinical neurological and cognitive dysfunction that can only be identified through a neurophysiological and neuropsychological evaluation because these disciplines can spot preclinical CNS abnormalities [27].

Sixty SLE cases were included in our current study. NPSLE and non-NPSLE cases were separated into two groups, 30 participants made up the study's control group.

The P300 latency was significantly prolonged in SLE compared to the control group, which was a key finding of the current study, This finding highlights the idea that SLE is a source of cognitive impairment, which has been shown in numerous research studies [28-30].

Our study demonstrated a non-significant difference in P300 latencies between non-NPSLE patients and NPSLE patients, which was consistent with other research from Poland and Japan [31, 32] that found no significant difference in the mean P300 values between the NPSLE and non-NPSLE categories [33]. Furthermore, P300 latencies have been proposed as a biomarker for additional neurological pathology in non-NPSLE cases, and ERPs can be used to detect subclinical deficits in cognitive skills [16].

In all SLE patients, there was a P300 latency that was significantly prolonged along with a poorer MoCA score, indicating a strong relationship between P300 and MoCA. Another Egyptian study's findings agreed with ours [16, 34]. According to P300 data, there may be discrepancies in patient demographics, methodology, or apparatus between research studies.

Regarding our current investigation, there was no association between corticosteroid dose and P300 aberrations.

In patients with SLE, cognitive impairment is a common issue. In our investigation, utilizing the MOCA exam, we found significant cognitive dysfunction in all SLE patients compared to the control group, which was consistent with previous research [25]. Regardless of education level, a highly statistically significant difference between SLE patients and control people was found in a different investigation [35]. When compared to the control group, cognitive impairment was found to be more pronounced in non-NPSLE patients utilizing MoCA. This indicates that a mild CNS disease may be present.

Results from a prior study that we concurred with indicated that non-NPSLE patients had more pronounced cognitive dysfunction than the control group.

In all SLE patients, the P300 latency was significantly prolonged along with a poorer MoCA score. indicating that P300 and MoCA have a strong relationship. Our study's findings agreed with those of another Egyptian study. In our investigation, we discovered that there was a strong negative association between the MOCA and SLEDAI scores in SLE patients, indicating a high risk for disease activity. No association between MoCA and SLEDAI score was discovered in previous research. The findings of our investigation, which were consistent with those of another study, showed no connection between the dosage of steroids and cognitive dysfunction[16, 34].

The same findings from a previous study were confirmed: anti-double-stranded DNA antibodies related to extended P300 Latency, which represents cognitive impairment [32].

In the current investigation, we discovered that anti-RNP antibodies are not associated with a longer P300 latency in SLE patients. An earlier study, in agree with ours, discovered a negative correlation between anti-nucleosome antibodies presence and p300 latency [35].

According to multiple publications, autoantibodies typically found in the serum of SLE patients, including anti-RNP and anti-sm antibodies may have a role in the development of neuropsychiatric symptoms, albeit the exact mechanism is yet unknown [36].

In contrast to our study, a previous study showed that anti-histone antibody markers were prevalent in NPSLE patients detected by ELISA [37].

In contrast to a previous study that found ant phospholipid antibodies to be a risk factor for abnormal electrophysiological parameters that could be explained by ischemic cranial neuropathy caused by venous thrombosis and multifocal microinfarcts, anti-APS antibodies were not found to be a risk factor for ERP abnormalities in SLE patients in our current study [14, 38].

In line with a recent investigation that identified no connection between anti-ribosomal P antibodies and cerebral symptoms in SLE patients, our current study demonstrates that anti-ribosomal -p antibodies are not a risk factor for prolonged p300 latency in SLE patients, as opposed to another study that found aberrant electrophysiological parameters linked to the presence of anti-ribosomal -p antibodies [39].

According to a previous study, anti-ribosomal -p antibodies can directly affect neuronal cells through intrathecal production or by crossing a permeabilized blood-brain barrier. This suggests that these antibodies cause diffuse NP events (such as psychosis, depression, and cognitive impairment) by having an impact on neuronal cells [40].

The small sample size was considered as a limitation of our study.

Conclusion

Sixty SLE cases were classified into NPSLE and non-NPSLE instances in the study. Early therapy is made possible by the P300's ability to detect cognitive impairment in subclinical phases. Autoantibodies were discovered to be a risk factor for P300 abnormalities, indicating that anti-double-stranded DNA antibodies need to be regularly watched for possible central nervous system problems.

Recommendations:

- Further studies to detect future clinically manifest CNS dysfunction and other neurological events in Non-NPSLE cases with abnormal P300 and so, using ERP as a neurophysiological biomarker for NPSLE.

- Further studies are needed for patients with prolonged p300 latency to show the effect of change of treatment protocols.
- Further prospective studies are recommended to show autoantibodies related to neuropsychiatric problems in SLE using ERP as an objective method.

Abbreviations:

- ACR: American college of rheumatology
- AEPs: auditory evoked potentials
- CD: cognitive dysfunction
- CMAP: compound motor action potentials
- CNS: central nervous system
- CRP: c-reactive protein
- ENAs: extractable nuclear antigens
- EP: evoked potentials
- ERP: event-related potentials
- LN: lupus nephritis
- MoCA: The Montreal Cognitive Assessment Questionnaire
- NP: neuropsychiatric
- NPSLE: neuropsychiatric systemic lupus erythematosus
- PNS: peripheral nervous system
- SLE: systemic lupus erythematosus
- SLEDAI: systemic lupus erythematosus diseases activity index
- SLICC: SLE Collaborating Clinics Criteria
- SNAP: sensory nerve action potentials.

Ethics approval and consent to participate

- The study was approved by the Research Ethical Committee, Faculty of Medicine Sohag University.
- Ethical committee reference number: soh.med 20.12.7
- Written consent was taken from all patients.

All authors consent to the publication of this research.

Declaration

Competing interest: the authors declare that they have no conflict of interest .

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Availability of data and materials.

The data sets used and or analysed during the current study are available from the corresponding author on reasonable request.

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