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Correlation between Anti- DNA/N- methyl- D- aspartate Receptor 2 antibodies and Systemic Lupus Erythematosus

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Abstract

Background:Self-reactive antibodies are a characteristic of systemic lupus erythematosus [SLE]. These autoantibodies may attack any organ or tissue in the body causing organ failure. One class of anti-DNA antibodies, known as anti-DNA/N-methyl-D-aspartate receptor 2 [anti-DNA/NR2] antibodies, also interacts with the NR2 subunit [anti-NR2] of N-methyl-D-aspartate receptors [NMDARs]. Research suggests that anti-NMDAR antibodies contribute to the pathophysiology of SLE-related emotional and cognitive dysfunction.Objective:The goal of this study was to evaluate the prevalence and severity of systemic lupus erythematosus in individuals with anti-DNA/N-methyl-D-aspartate receptor 2 [NR2] antibodies.Methodology: 60 SLE patients and 30 healthy controls had serum samples taken. Anti-NR2 antibodies in the serum were tested using an ELISA kit.Results: The average serum anti-NR2 antibody level in SLE patients was 34.10 ng/ml, whereas the level in healthy controls was only 11.60 ng/ml with a statistically significant difference [P<0.001].Serum anti-NR2 can significantlydiscriminate between SLE patients and healthy subjects, with diagnostic ability at best cut off value 13.26 ng/ml with high sensitivity and specificity.Conclusion:Serum anti-NR2 can be used as a new biomarker for SLE.

1. Introduction

Systemic lupus erythematosus, or SLE, is a chronic autoimmune systemic illness with a wide range of possible symptoms and a convoluted origin. From a 50% five-year survival rate in the 1950s, it is now over 90%, demonstrating significant progress over time **[1].** Controlling disease activity, improving health-related quality of life, minimising drug-related adverse events, and protecting against harm have all become important goals of care for patients with SLE **[2].**

Self-reactive antibodies are a characteristic of systemic lupus erythematosus, and these antibodies may attack any organ or tissue in the body. Eventually, these antibodies can form immune complexes, which can collect in any organ, causing organ failure **[3].**

The interaction between tight disease management and avoiding treatment associated side effects may be highly problematic in SLE since damage can be attributable to both non-modifiable variables [such as age and ethnicity] and modifiable ones [such as disease activity and immunosuppressive drugs]. Clinical studies have made damage prevention a primary therapeutic goal in the treatment of SLE **[4].**

One class of anti-DNA antibodies, known as anti-DNA/N-methyl-D-aspartate receptor 2 [anti-DNA/NR2] antibodies, also interacts with the NR2 subunit [anti-NR2] of N-methyl-D-aspartate receptors [NMDARs]. Research suggests that anti-NMDAR antibodies contribute to the pathophysiology of SLE-related emotional and cognitive dysfunction **[5].**

Our research team set out to examine whether and how anti-DNA/N-methyl-D-aspartate receptor 2 [NR2] antibodies were present in the blood of patients with systemic lupus erythematosus.

2.Content and approaches

Subjects included [60] patients with SLE who met the EULAR/ACR diagnostic criteria for SLE in 2019 **[6]** and were seen in the in-patient and out-patient clinics at Benha University Hospitals' Rheumatology, Rehabilitation& Physical Medicine Department; and [30] age- and sex-matched apparently healthy volunteers used as a control group.

Before being recruited, all subjects supplied written informed permission, and the research was approved by the local ethics committee at Benha College of Medicine.

All patients were evaluated clinically, including a thorough history and physical examination.

Routinelaboratory investigations were done besides anti-dsDNA antibodies.

We used the Human anti-NMDAR Antibody [anti-N-methyl-D-aspartic Acid receptor Antibody] Cat.No: EH4166 from [Fine Test, Wuhan, China] to measure anti-DNA/N-methyl-D-aspartate receptor antibodies in the serum.

The Statistical Software for the Social Sciences was used for the statistical analyses [IBM Corp. Released 2017. IBM SPSS

Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.]. Analysis of the correlation between two qualitative variables was performed using the Chi-Square test and the Student T Test was used to determine statistical significance between the means of the two research groups. Receiver operating characteristic [ROC] curves are used to assess the accuracy of quantitative diagnostic measures that use binary classification to make diagnoses. Maximum area under the curve [AUC] was used to determine the best cutoff, and Pearson's correlation was used to determine the strength of the relationships between variables. The cutoff for significance was set at P<0.05.

3.Results

This study included [60] SLE patients and [30] age and sex matched apparently healthy volunteers as control group. Fifty-four SLE patients [90%] were females and 6 patients [10%] were males [Fig.1]. Their ages ranged from 17 to 51 years [Mean ± SD 28±8 years].Twenty-four healthy subjects [80%] were females and 6 healthy subjects [20%] were males. Their ages ranged from 19 to 42 [Mean ± SD 29.73±7 years]. No statistically significant difference was reported between the studied groups regarding age [P= 0.246] and sex [P=0.324] distribution Table (1).

Table (1) Comparison between SLE patients and controls regarding demographic data.

		Patients [No.=60]	Controls [No.=30]	Test	P
Gender	**Female**	54[90%]	24[80%]	X2=1.731	0.324
	Male	6[10%]	6[20%]		
Age	**Mean± SD**	28±8	29.73±7	Z=1.161	0.246
	Range	17-51	19-42		

X^2=Chi-Square, Z=Kruskalwallis.

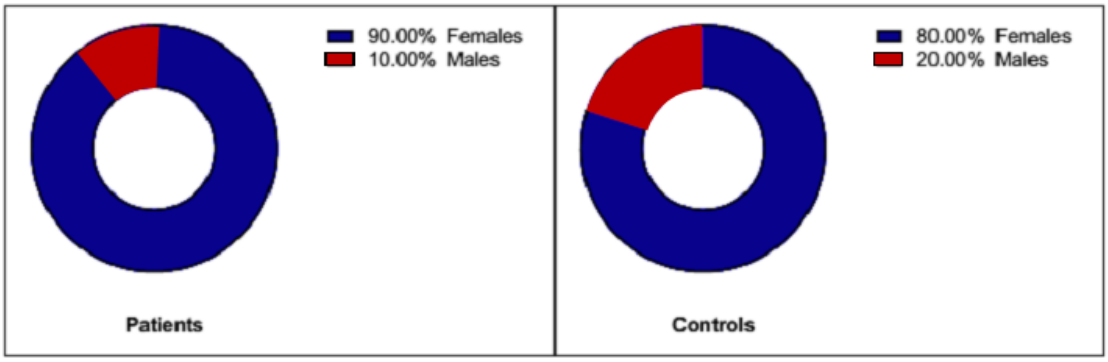

Fig.(1): Comparison between patients and controls regarding sex distribution.

Comparison between SLE patients and controls regarding serum level of anti-NR2 antibody showed that serum level of anti-NR2 antibody in SLE patients was significantly higher [P<0.001] than its level in healthy controls, mean level in SLE patients was [34.10 ng/ml] while it measured [11.6 ng/ml] in control group Table (2), Fig. (2).

Table (2) Comparison between SLE patients and controls regarding serum anti-NR2 level.

Anti-NR2 [ng/ml]	Patients [No.=60]	Controls [No.=30]	Test Mann whitney	P
Mean ±SD	34.10±12.45	11.60±5.09	Z=7.096	<0.001* [HS]
Range	17.46-53.27	6.94-27.2		

HS: Highly Significant P<0.001.

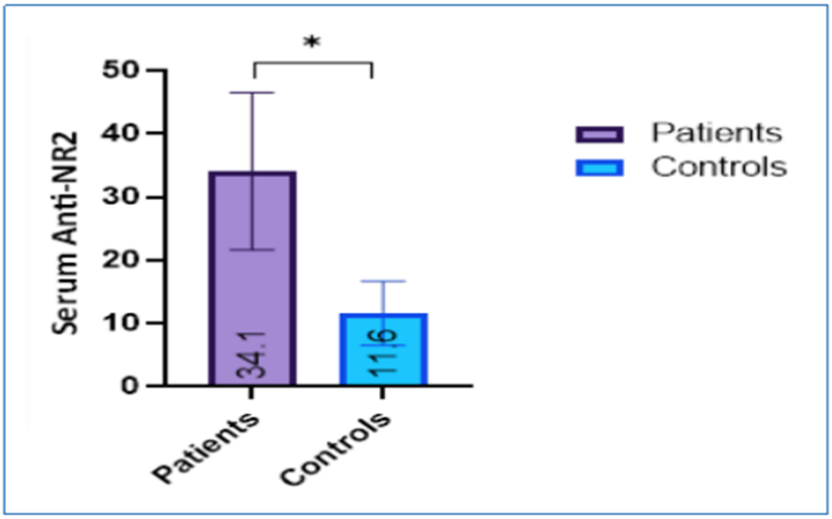

Fig. (2) Serum anti-NR2 level comparison between SLE patients and controls.

ROC curve of serum anti-NR2 was conducted for discrimination between SLE patients and healthy subjects. Serum anti-NR2 showed high accuracy area under the curve [AUC] [0.961] at the 95% CI, with diagnostic ability at best cut off value [13.26 ng/ml] with good sensitivity and specificity Table (3) , Fig. (3).

Table (3): Validity of serum anti-NR2 for discrimination of patients from control group:

Anti-NR2 [ng/mL]					
AUC	95% CI	P	Cut off	Sensitivity [%]	Specificity [%]
0.961	0.897-0.990	<0.001*	13.26	100	86.67

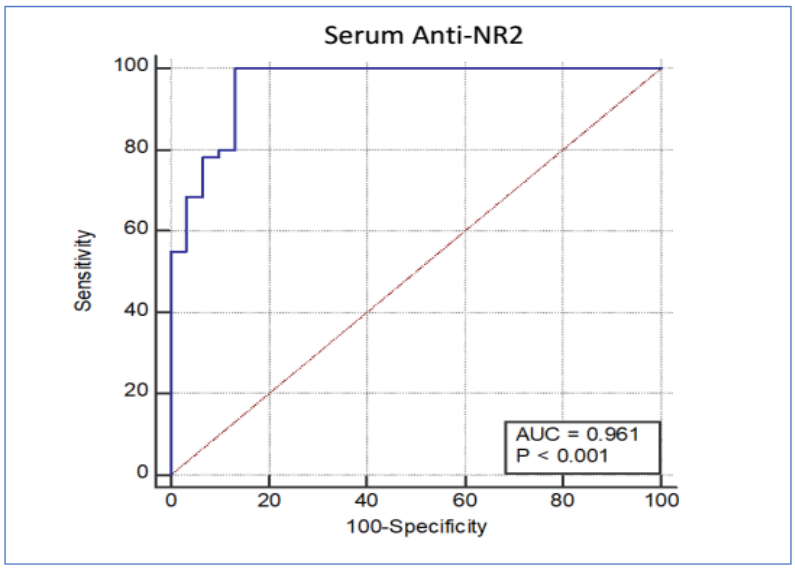

Fig. (3)Validity of serum anti-NR2 for discrimination of SLE patients from control group.

4. Discussion

Autoimmune connective tissue disease systemic lupus erythematosus [SLE] is more frequent in young women and is characterised by flare-ups and remissions that cause progressive organ damage and high death rates **[7]**.

The clinical and immunological symptoms of SLE were different across sexes in an Egyptian research,but had certain similarities with studies conducted in other countries. The disease expression in Egyptian SLE patients was found to be similar to that in patients of other ethnicities, but with less frequent

neuropsychiatric involvement in the first attempts to research the clinical features of Egyptian SLE patients **[8]**.

Excessive B- and T-cell activation, autoantibody synthesis, and immunological complex formation have all been implicated in SLE pathogenesis, although the exact causes of this autoimmune disease remain unknown. Patients with alopecia and nephritis in particular showed signs of oxidative stress, which was linked to disease activity in SLE **[9].**

While anti-DNA antibody positivity is associated with SLE disease activity and glomerulonephritis, the link to neurological illness is less evident **[10]**. As shown by the Diamond group the murine anti-DNA can detect a particular sequence ['DWEYS'] included in the N-methyl-D-aspartate [NMDA] receptors NR2a and NR2b **[11]**.Faustet al.**[12]** found that passive transfer of anti-DNA/NR2 antibodies to healthy mice increased neuronal death.Moreover, hippocampus neuron injury and memory loss were brought on by active vaccination with the DWEYs, followed by the rupture of the BBB by lipopolysaccharide **[13]**.

The purpose of this research was to examine the prevalence of anti-NR2 antibodies in the blood of people with systemic lupus erythematosus.

Sixty people with SLE and thirty healthy controls participated in this research. The mean serum anti-NR2 antibody level in SLE patients was 34.10 ng/ml, significantly higher than the level in healthy controls [11.6 ng/ml]. This increase was statistically significant [P0.001].

Our findings corroborated the findings of Yang et al. **[14]**, who examined the levels of anti-NR2A in 107 SLE patients with and without NP symptoms, and showed that the SLE patients had substantially higher levels of anti-NR2A compared to the control group.

Consistent with our findings is the meta-analysis by Tay et al., **[15]**, which included 17 studies reporting the presence or absence of anti-NR2A/B antibodies in a total of 2,212 patients with systemic lupus erythematosus [SLE], 66 patients with Sjögren's syndrome [SS], and 538 healthy controls [HCs]. The pooled prevalence of anti-NR2A/B antibodies in SLE patients was 24.6% [95% CI 18.5-32.0%] and in SS patients it was 19.7% [95% CI 11.8-31.0%], but in HCs it was only 7.6% [95% CI 4.6-12.4%] [p = 0.001].

More than that, Nowling et al. **[16]** compared 12 individuals with juvenile idiopathic arthritis to 24 patients with SLE at the same age [JIA]. Anti-NR2 serum antibody levels were substantially greater in children with SLE than in those with JIA.

Our findings are limited by the very small sample size of patients analysed. The cross-sectional approach is also a drawback since it cannot determine causal relationships. To further identify the function of anti-MNDAR in the aetiology of NPSLE, longitudinal studies with a greater number of patients are suggested.

5. Conclusion

The results of this research reveal that serum anti-NR2 levels are significantly elevated in individuals with SLE, suggesting that serum anti-NR2 may serve as a potential bio

Refrences

[1] Saleki K, Shirzad M, Banazadeh M, et al. Lupus and the Nervous System: A Neuroimmunoloigcal Update on Pathogenesis and Management of Systemic Lupus Erythematosus with Focus on Neuropsychiatric SLE. IntechOpen; 2022.

[2] Barber MRW, Drenkard C, Falasinnu T, et al. Global epidemiology of systemic lupus erythematosus. Nat Rev Rheumatol. 2021;17[9]:515-532.

[3] Sato S, Temmoku J, Fujita Y, et al. Autoantibodies associated with neuropsychiatric systemic lupus erythematosus: the quest for symptom-specific biomarkers. Fukushima J Med Sci. 2020;66[1]:1-9.

[4] Ameer MA, Chaudhry H, Mushtaq J, et al. An Overview of Systemic Lupus Erythematosus [SLE] Pathogenesis, Classification, and Management. Cureus. 2022;14[10].

[5] Manca E. Autoantibodies in Neuropsychiatric Systemic Lupus Erythematosus [NPSLE]: Can They Be Used as Biomarkers for the Differential Diagnosis of This Disease? Clin Rev Allergy Immunol. 2022;63[2]:194-209.

[6] Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol Hoboken NJ. 2019;71[9]:1400-1412.

[7] Tsokos GC. Autoimmunity and organ damage in systemic lupus erythematosus. Nat Immunol. 2020;21[6]:605-614.

[8] Gheita TA, Noor RA, Abualfadl E, et al. Adult systemic lupus erythematosus in Egypt: The nation-wide spectrum of 3661 patients and world-wide standpoint. Lupus. 2021;30[9]:1526-1535.

[9] Suurmond J, Atisha-Fregoso Y, Marasco E, et al. Loss of an IgG plasma cell checkpoint

in patients with lupus. J Allergy ClinImmunol. 2019;143[4]:1586-1597.

[10] Schwartz N, Stock AD, Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. Nat Rev Rheumatol. 2019;15[3]:137-152.

[11] DeGiorgio LA, Konstantinov KN, Lee SC, Hardin JA, Volpe BT, Diamond B. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. Nat Med. 2001;7[11]:1189-1193.

[12] Faust TW, Chang EH, Kowal C, et al. Neurotoxic lupus autoantibodies alter brain function through two distinct mechanisms. ProcNatlAcadSci U S A. 2010;107[43]:18569-18574.

[13] Chang EH, Volpe BT, Mackay M, et al. Selective Impairment of Spatial Cognition Caused by Autoantibodies to the N-Methyl-D-Aspartate Receptor. EBioMedicine. 2015;2[7].

[14] Yang Y, Yuan C, Shen SQ, et al. Autoantibodies to NR2A Peptide of the Glutamate/NMDA Receptor in Patients with Seizure Disorders in Neuropsychiatric Systemic Lupus Erythematosus. Mediators Inflamm. 2017;2017:5047898.

[15] Tay SH, Fairhurst AM, Mak A. Clinical utility of circulating anti-N-methyl-d-aspartate receptor subunits NR2A/B antibody for the diagnosis of neuropsychiatric syndromes in systemic lupus erythematosus and Sjögren's syndrome: An updated meta-analysis. Autoimmun Rev. 2017;16[2]:114-122.

[16] Nowling TK, Kral M, Wolf B, Gilkeson G, Ruth NM. Formal neurocognitive function and anti-N-methyl-D-aspartate receptor antibodies in paediatric lupus. Lupus Sci Med. 2021;8[1]:e000462.