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ORIGINAL ARTICLE

Brain Metabolic Alteration and Neuropsychiatric Dysfunction in Childhood – onset Systemic Lupus Erythematosus

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ABSTRACT

Background: Neuropsychiatric Lupus Erythematosus (NPSLE) is the main cause for morbidity and mortality in Systemic Lupus Erythematosus (SLE) .This study aimed to early diagnosis of neuropsychiatric dysfunctions in childhood - onset SLE by Magnetic Resonance Spectroscopy (MRS).

Methods: This study was observational descriptive cross sectional study done in Nephrology unit, Pediatric department, zagazig university hospital from March 2017 to March 2018. Thirty patients with SLE were randomly selected, aged from 9-17 years old and divided into two groups .Group one was eleven cases with neuropsychiatric manifestations and group two was nineteen cases without neuropsychiatric manifestations. MRS used to assess any metabolic brain dysfunction causing neuropsychiatric disorders and the results of MRS readings of the two groups were compared with each others.

Results: One hundred percent of patients in the study shows abnormal MRS findings instead of only, 36.7% of the studied group shows neuropsychiatric manifestations. There were non- significance differences between both studied groups in MRS findings. There was statistical significance increase in the NPSLE cases than others according to the presence of lupus anti -coagulant antibody.

Conclusion: NPSLE can be diagnosed easily by MRS for early management which improves the quality of patient's life. MRS can also detect disease activity very early for reevaluation of management and the efficacy of treatment.

INTRODUCTION

Systemic Lupus Erythematous is chronic multiorgan disease involving skin, blood vessels, kidney, joints, hematological system and central nervous system. It is caused by the inflammation with circulating autoimmune antibodies, immune dysregulation and immune complex formation. **[1].** Its incidence is 0.5-0.6 cases per 100000 persons in patients younger than 15 years. **[2]** It is higher in female more than male (approximately 4:1) before puberty. **[3]**

NPSLE is caused by combination of immunological and vascular mechanisms.it may show elevation of serum levels of lupus anticoagulant (LA), anti-cardiolipin, anti-ribosomal P and anti-phospholipid antibodies**. [4]**

According to American College of Rheumatologists (ACR), NPSLE include mood disorders, acute confusional state, cognitive dysfunction, psychosis and anxiety. **[5]**

Magnetic Resonance spectroscopy (MRS) plays an important role for detection of any brain metabolic disorders in SLE to assess the effectiveness of treatment**. [6]** MRS is non- invasive tool depend on measure of metabolic levels of some metabolites and detect any disturbance of them such as N-acetyl aspartate (NAA), Creatine (Cr), Choline (Cho) ,Myoinositol (MI) ,Glutamate (GLU) and Lactate (Lac) and calculate some metabolite ratios as (NAA/Cr) , (NAA/Cho) and (Cho/Cr) ratios**. [7]** MRS in SLE shows decrease in NAA/Cr ratio in the white matter in comparison to normal white matter in a healthy brain**. [8]** The aim of this study is to diagnose the neuropsychiatric dysfunctions in Childhood - onset SLE by Magnetic Resonance Spectroscopy (MRS) early before their diagnosis clinically.

METHODS

This observational descriptive cross-sectional study was done in nephrology unit, pediatric department, and Zagazig university hospital in the period from March 2017 to March 2018.

Thirty cases of SLE are randomly selected then divided into 2 groups according to the presence or absence of neuropsychiatric manifestations by clinical evaluation (history and examination).

Cases of SLE are selected randomly from outpatient follow up clinic of Nephrology unit, pediatric department, zagazig university hospital with exclusion of patients more than 18 years, patients suffered from other medical conditions as cerebral palsy and mental retardation, or presence of any contraindications to perform Magnetic Resonance Imaging (MRI) as prosthetic valve.

Group one includes 11patients of SLE with neuropsychiatric manifestations (NPSLE) and group two include 19 patients of SLE without neuropsychiatric manifestations. (Non-NPSLE). All patients were subjected to full history, clinical examination, and laboratory investigations as (complete blood count, lupus anti- coagulant Ab, protein/creatinine ratio and renal biopsy).

All patients were subjected to radiological investigations include

a) Conventional MRI brain: MRI was performed using 1.5 tesla Philips scanner T1WI and T2WI sequences were obtained in axial, sagittal and coronal planes. With sedation according to age.

b) Brain MR spectroscopy. Single voxel MR spectroscopy was placed white matter. Voxel size was chosen to provide adequate signal and to be small enough to prevent partial volume averaging of adjacent structures .voxel sizes varied between 1.5and 2 cm .The result is frequency curve illustrating different metabolites (NAA, Cho , MI, Lac, GLU and CR) as well as ratios (NAA/Cho, CHO/CR, and NAA/CR).

Ethical declaration

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the world Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis: Data were analyzed by SPSS software, version 22.0 (SPSS Inc, 2013).Qualitative data are represented as numbers and percentage but quantitative data are represented as as mean ± SD. A $\chi 2$test was used to determine the differences between frequencies (qualitative variables) and independent t test to compare between means of Independent two groups of parametric variables. Mann-Whinty test used to compare two groups of independent non parametric variables. Correlation was done by Pearson's correlation. P-value was set at equal or less than0.05 for significant results and p less than 0.001 for highly significant results.

RESULTS

There was statistical significance increase in age among NPSLE compare to non-NPSLE.but there were non- significance difference between the studied groups in sex and family history as in **(Table 1)**.

There was non- significance difference between the two studied groups in the duration of the disease and the duration of steroid therapy but, there were statistical significance increase in SLEDAI and mean of hypertension among the NPSLE group compared to non NPSLE as in **(Table 2).**

There was non -significance difference among the two studied groups in the initial presentation of SLE as in **(Table 3).**

By the comparison between the two studied groups in **(Figure 1)**, we detect statistical significance increase in frequency of all neurological manifestations in NPSLE.

There was statistical significance increase in the frequency of positive lupus anticoagulant among NPSLE cases in comparison to non- NPSLE as in **(figure 2)**.

MRS findings in SLE cases of the studied groups show decrease of mean NAA, Cr, Cho, MI, GLU, Lac, NAA/Cr ratio, and NAA/Cho ratio but increase Cho/Cr as in **(Table 4).**

There was non- statistical significance difference between the two studied groups in MRI findings (conventional MRI and MRS) as in **(Table 5).**

Table (1): Relation between NPSLE and Socio-demographic characteristics among the studied group:

Variable		Non NPSLE (n=19)		NPSLE (n=11)		T	P
Age:	Mean ± SD Range	10.82 ± 2.27 9 – 17		14.32 ± 1.89 11 – 17		**4.54**	**<0.001 ****
Sex:	Female(n=23) Male (n=7)	16 3	69.6 42.9	7 4	30.4 57.1	1.65	0.20 NS
Family history:	-ve (n=18) +ve (n=12)	11 8	61.1 66.7	7 4	38.9 33.3	0.10	0.76 NS

Table (2): Relation between NPSLE and Clinical data among the studied groups:

Variable		**Non NPSLE (n=19)**		**NPSLE (n=11)**		**Test**	**P**
Duration of disease: (years)	Mean ± SD Median (Range)	5.11 ± 2.49 5 (2 – 9)		5.18 ± 1.08 5 (4 – 7)		MW 0.57	0.57 NS
Duration of steroid therapy: (months)	Mean ± SD Median (Range)	50.37 ± 22.50 60 (20 – 84)		54.91 ± 13.75 60 (40 – 84)		MW 0.13	0.90 NS
SLEDA:	Mean ± SD Range	53.16 ± 17.76 34 - 80		66.27 ± 13.52 43 - 80		**T** **2.11**	**0.04***
SBP: (mmHg)	Mean ± SD Range	130.26 ± 18.06 100 - 150		140.91 ± 9.44 130 - 150		**T** **2.15**	**0.04***
DBP: (mmHg)	Mean ± SD Range	85.53 ± 12.57 70 - 100		96.36 ± 3.93 90 - 100		**T** **2.76**	**0.01***
Variable		**No**	**%**	**No**	**%**	χ^2	**P**
HPT	No (n=6) Yes (n=24)	6 13	100 54.2	0 11	0 45.8	**4.34**	**0.04***

SLEDA: Systemic Lupus Erythematosus Disease Activity. **HPT:** Hypertension.
SBP: Systolic blood pressure**.** **DBP:** Diastolic blood pressure.

Table (3): Relation between NPSLE and Initial manifestations of SLE in the studied group

Variable		**Non NPSLE (n=19)**		**NPSLE (n=11)**		**Test**	**P**
Manifestations	**Variable**	**No**	**%**	**No**	**%**	χ^2	**P**
Cutaneous manifestations	No (n=5) Yes (n=25)	2 17	40 68	3 8	60 32	1.41	0.24 NS
Articular	No (n=6) Yes (n=24)	3 16	50 66.7	3 8	50 33.3	0.57	0.45 NS
Renal	No (n=23) Yes (n=7)	16 3	69.6 42.9	7 4	30.4 57.1	**1.65**	**0.20** **NS**
Hematological	No (n=9) Yes (n=21)	5 14	55.6 66.7	4 7	44.4 33.3	0.34	0.56 NS

Table (4): MRI findings among the studied group

	Variable		**(n=30)**
MRS	N acetyl aspartate: (ppm)	Mean ± SD Median (Range)	0.42 ± 0.40 0.20 (-0.05-1.07)
	Creatine: (ppm)	Mean ± SD Median (Range)	0.24 ± 0.33 0.25 (-0.18 - 0.81)
	Choline: (ppm)	Mean ± SD Median (Range)	0.32 ± 0.20 0.34 (0 – 0.68)
	GLU: (ppm)	Mean ± SD Median (Range)	0.07 ± 0.14 0.08 (-0.28 - 0.26)
	MI: (ppm)	Mean ± SD Median (Range)	0.05 ± 0.13 0.004 (-0.12 – 0.29)
	Lactate: (ppm)	Mean ± SD Median (Range)	0.19 ± 0.26 0.15 (-0.03 – 0.77)
	NAA/CR	Mean ± SD Median (Range)	1.04 ± 0.58 1.1(-0.20 – 1.91)
	NAA/CHO	Mean ± SD Median (Range)	1.02 ± 0.91 0.72 (-0.31 – 2.87)
	CHO/CR	Mean ± SD Median (Range)	1.43 ± 1.55 0.83 (0 – 5.3)
	Variable		**No** **%**
	NAA/CR	Normal	6 20

Variable			(n=30)	
		Abnormal	24	80
	NAA/CHO	Normal	13	43.3
		Abnormal	17	56.7
	CHO/CR	Normal	23	76.6
		Abnormal	7	23.3
Conventional	MRI:	Normal	23	76.7
		Abnormal	7	23.3

NAA: N-acetylaspartate. **CR**: Creatine**.** **CHO**: Choline. **GLU**: Glutamate.
MI: Myoinositol. **MRS**: Magnetic Resonance Spectroscopy.
MRI: Magnetic Resonance Imaging.

Table (5): Relation between NPSLE and MRI findings among the studied group

Variable		Non NPSLE (n=19)		NPSLE (n=11)		MW	P
N acetyl aspartate: (ppm)	Mean ± SD Median (Range)	0.48 ± 0.38 0.20 (-0.05 – 0.97)		0.51 ± 0.45 0.20 (0.09 – 1.07)		1.38	0.17 NS
Creatine: (ppm)	Mean ± SD Median (Range)	0.25 ± 0.22 0.20 (-0.18 – 0.48)		0.21 ± 0.48 0.16 (-0.18-0.81)		0.78	0.44 NS
Choline: (ppm)	Mean ± SD Median (Range)	0.26 ± 0.16 0.29 (0-0.52)		0.41 ± 0.22 0.30 (0.13 – 0.68)		1.82	0.07 NS
GLU: (ppm)	Mean ± SD Median (Range)	0.04 ± 0.16 0.05 (-0.28 – 0.26)		0.11 ± 0.05 0.09 (0.08 – 0.21)		1.81	0.08 NS
MI: (ppm)	Mean ± SD Median (Range)	0.05 ± 0.16 0.003(-0.12-0.29)		0.06 ± 0.09 0.07 (-0.03-0.16)		0.87	0.39 NS
Lactate: (ppm)	Mean ± SD Median (Range)	0.18 ± 0.29 0.02 (-0.03 – 0.77)		0.14 ± 0.08 -0.03 (-0.03-0.20)		1.79	0.08 NS
NAA/CR	Mean ± SD Median (Range)	0.85 ± 0.55 0.86 (-0.20-1.39)		1.07 ± 0.49 1.02 (0.68 - 1.91)		1.83	0.07 NS
NAA/CHO	Mean ± SD Median (Range)	0.97 ± 1.07 0.92 (-0.31 – 1.58)		1.10 ± 0.57 1.08 (0.20-2.87)		0.44	0.66 NS
CHO/CR	Mean ± SD Median (Range)	1.34 ± 1.71 1.18 (0 – 5.3)		1.59 ± 1.28 1.2 (0.83 – 5.30)		1.34	0.18 NS
Variable		**No**	**%**	**No**	**%**	χ^2	**P**
NAA/CR	Normal (n=6) Abnormal (n=24)	4 15	66.7 62.5	2 9	33.3 37.5	0.04	0.85 NS
NAA/CHO	Normal (n=13) Abnormal (n=17)	7 12	53.8 70.6	6 5	46.2 29.4	0.89	0.35 NS
CHO/CR	Normal (n=23) Abnormal (n=7)	16 3	69.6 42.9	7 4	30.4 57.1	1.65	0.20 NS
Conventional MRI:	Normal (n=23) Abnormal (n=7)	16 3	69.6 42.9	7 4	30.4 57.1	1.65	0.20 NS

Sd: Standard deviation MW: Mann Whitney test χ^2: Chi square test
NS: Non significant (P>0.05)

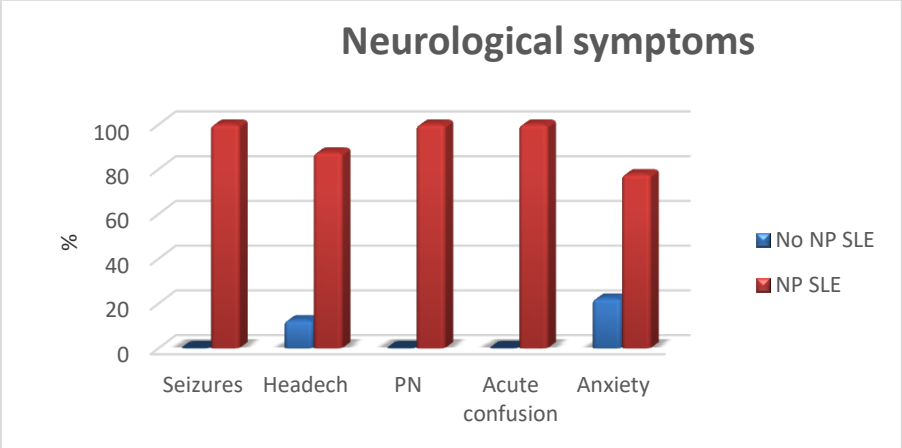

Figure (1): Relation between NPSLE and neurological symptoms of the studied group.

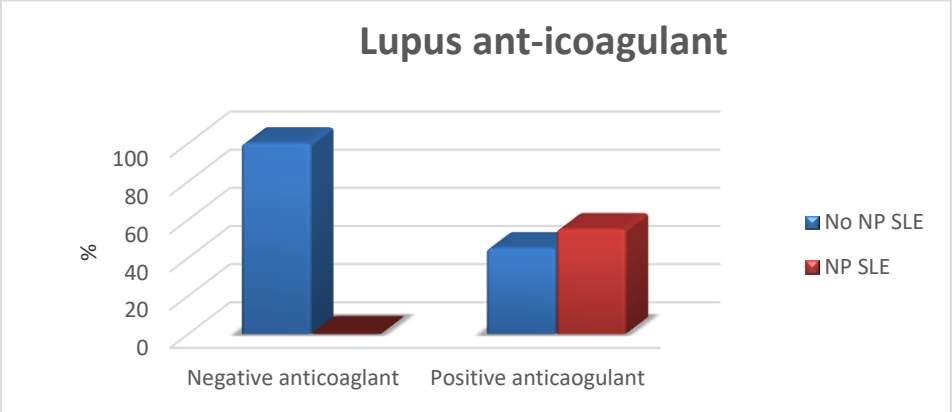

Figure (2): Relation between NPSLE and Lupus anti-coagulant among the studied group.

DISCUSSION

Systemic Lupus Erythematous (SLE) is an autoimmune multi-organs disease which affects nervous system, skin, kidney, joints, lung, cardiovascular, and hematological systems.

Previously, Neuropsychiatric SLE (NPSLE) cannot be diagnosed laboratory or radiologically and only suspect the diagnosis by the clinical manifestations and exclusion of any causes of NPSLE.

But now, there is a hopeful tool for easy and early diagnosis of NPSLE which is Magnetic Resonance Spectroscopy (MRS).

This study aimed to explain the role of brain MRS in the early diagnosis of NPSLE and the relations of NPSLE with duration of the disease, duration of the steroid therapy, SLEDA index, hypertension, and the presence of lupus anticoagulant antibodies.

There was a relation between NPSLE and socio-demographic characteristics among the studied group and there was statistical significance increase in age among cases had NPSLE compared with non-NPSLE cases. This may be due to the prolonged exposure to complication of disease and side effects of steroid therapy and these results mismatched with **Sarbu N et al., [1]** who shows that age is independent predictors for NPSLE.

Also, there was no significant difference among the studied groups in sex and family history which matched with Murphy G et al., [9] who show that the association between gender and NPSLE had limited evidence.

This study show non- significant differences between NPSLE cases and non NPSLE cases in duration of disease, duration of steroid therapy. But there was statistically significant increase in hypertension and SLEDA index. These may be due to increase frequency of hypertension and increase SLEDA score cause neuropsychiatric dysfunction or worse NPSLE manifestation by increase the risk for atherosclerosis due to HPN, inflammation and vasculopathy. These results matched with Conti F et al., and Ho CS. [10, 11]

This study show non –significant difference between the studied groups in the initial presentation of the disease. But, there was statistical significance increase in the frequency of all neurological manifestations in NPSLE group compared with non-NPSLE cases and this matched with Watson P et al., [12].

There was statistical significance increase in the frequency of positive Lupus anticoagulant antibody among the studied groups because Lupus anticoagulant antibodies are responsible for

NPSLE by microangiopathy and thrombosis formation. This matched with Ho CS and Sciascia S et al., [11, 13]. In this study, 100% of studied cases show abnormal brain MRS instead of only 23.3% of them show abnormalities in the conventional brain MRI. This mean that brain MRS plays an important role in the early diagnosis of neuropsychiatric dysfunctions in SLE before the appearance of neuropsychiatric manifestations and any abnormalities in the conventional brain MRI.

Brain MRS in the studied groups involve decrease mean of NAA (0.42), CR (0.24), CHO (0.32), GLU (0.07), MI (0.05) and LAC (0.19).Also, decrease mean of NAA/CR ratio (1.04), NAA/CHO ratio (1.02) and increase of CHO/ CR ratio (1.43).

Decrease NAA matched with Lim MK et al., [14] and this due to loss of neurons and neuronal dysfunction secondary to myelin breakdown. NAA is considered a marker for SLE disease activity.

Decrease CHO, MI, GLU and LAC may be due to ischemic changes of myelin, edema, necrosis, gliosis or cell loss. These matched with Santhakumari R et al., [15] but differed with Castellino G et al., [16] who observed increase of choline (CHO) concentration. Also, differed with Kaddah R O et al., [17] who show increase of CR and MI concentration. But in this study, CR decrease and this may be due to the changes in energy metabolite.

NAA/CR ratio was decreased in the studied cases due to small sized vessel injury causing axonal dysfunction but CHO/CR ratio was increased due to medium sized vessel injury. These abnormalities matched with Appenzeller S et al., [18].

This study show no statistical significance differences between NPSLE cases and non-NPSLE cases in conventional brain MRI and brain MRS findings and these confirm the importance of brain MRS for early diagnosis of any neurocognitive dysfunctions in SLE patients even before the appearance of neuropsychiatric manifestations. Also, detected the disease activity before its diagnosis clinically. These results matched with Godínez-Villanueva E et al., [19] who show no significant changes between NPSLE and non- NPSLE cases in the brain MRS findings but there were significant differences between both groups and normal control groups.

Limitation of the study

All the studied group on steroid therapy for long time, so the diagnosis and evaluation of their neuropsychiatric disorders was difficult to differentiate well if NPSLE was due to disease activity or steroid complications.

CONCLUSION

Previously, NPSLE is diagnosed clinically but, there are many vital tools for early and accurate detection of neuropsychiatric disorders for rapid management and improvement of quality of life such as brain MRS. Brain MRS helps also in early detection of SLE activity before it become obvious clinically and helps for evaluation of the efficacy of the treatment and the compliance of SLE patients by follow up with brain MRS to detect if the MRS findings transient and return to normal range or permanent and this give an idea about the poor outcome and prognosis.

RECOMMENDATION

Brain MRS may be used for early diagnosis of brain metabolic changes to expect the occurrence of NPSLE.Also, control of hypertension and hyper coagulation state decrease the risk for NPSLE.

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