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Cognitive Impairments in Children with Systemic Lupus and Neuropsychiatric Lupus

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Abstract

Objective: The aim of the present study was to determine neurocognitive profile in Children with Systemic (SLE) and Neuropsychiatric Lupus (NPSLE) describing differences in the seven cognitive areas proposed by the ACR (attention, memory, visuospatial processing, language, problem solving, processing speed, and executive function) between children with SLE and those with NPSLE and to understand the level of cognitive deterioration in children afflicted by SLE with and without neuropsychiatric changes.

Method: Children with SLE and with NPSLE were evaluated using the Wechsler Intelligence Scale for Children (WISC-IV) and some selected subtests of the Neuropsychological Assessment for Children (NAC), which allowed us to measure the 7 cognitive areas proposed by the ACR. Both, SLE and NPSLE children performances were compared to scores obtained by children without any affection.

Results: The area's most affected in the NPSLE group were attention, working memory, processing speed, memory, and visuospatial ability; in the SLE group, the area's most affected were processing speed, visuospatial ability, planning, and auditory memory.

Conclusion: Based on our findings, it is concluded that frequently in both groups cognitive decline is present since early stages of illness, being more important in the NPSLE group. These deficiencies are heterogenous and with a multi-domain pattern.

Keywords: Lupus; Neurocognitive; Neuropsychology; Children; Attention; Memory; Visuospatial

Introduction

Systemic Lupus Erythematosus (SLE) is a disease characterized by the appearance of multi-systemic clinical symptoms due to the presence of blood antibodies against one or more components of the nucleus and other intracellular antigens [1]. Then, SLE clinical manifestations are a result of tissue damage caused by immunoregulatory disorders, genetic components, hormonal influences, various exogenous agents and other clinical manifestations such as the presence of antiphospholipid antibody syndrome (APS) [2-4]. The most common symptoms are pain, joint inflammation, fever, weight loss, ganglionic cysts, changes in cardiac, renal, and pulmonary activity [1,5] as well as, neuropsychiatric manifestations [6-9].

The American College of Rheumatology (ACR) described 19 syndromes to specifically diagnose SLE in which neurological manifestations and general brain damage are common [10]. The latter can be accompanied by presentations of mental and behavioral disorders, such as psychosis and depression [6,7]. These ailments have been encompassed in the term Neuropsychiatric Systemic Lupus Erythematosus (NPSLE), where SLE patients manifesting compromises in their central and peripheral nervous system [8,9,11]. However, Neuropsychiatric manifestations in SLE patients exhibit substantial difficulties in diagnosis and treatment, because they are not specific [12-14]. The American College of Rheumatology [10] considers cognitive impairment as the clinical entity that best indicates NPSLE; hence, the diagnosis is confirmed when there is impairment in, at least, one cognitive area such as attention, memory, visuospatial processing, language, problem solving, processing speed, or executive function [15]. Several studies have found cognitive changes in the seven areas mentioned above in children and adults diagnosed with NPSLE [7]. Still, some studies stipulate that there is no specific pattern for the cognitive changes [16]. These differences in results are due to the pathophysiology underlying the different manifestations of NPSLE [3] and to the lack of consensus to the symptoms prevalence or intensity [17].

To determine if a patient with SLE is affected in one of these cognitive domains, the ACR proposes a battery of tests to measure cognitive functions in adults with SLE, but the ACR established that it could be used to evaluate adolescents as well [3]. To evaluate cognitive function in children with SLE and NPSLE, the tests are adjusted using standards to administer them in children [7]. In México, no studies have reported on cognitive impairment in children with SLE and NPSLE. Thus, it is our interest to understand the cognitive profile of children with SLE and NPSLE to determine if there are any differences between them to develop better neuropsychological rehabilitation programs.

Methods

Subjects

Eleven children diagnosed with SLE, were recruited (9 girls and 2 boys); 7 were diagnosed with NPSLE and 4 with SLE alone, in addition

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to patients, 11 children without any affection participated as a control group, (these were matched in age, school grade and gender to children in the clinical groups). The ages of the participants ranged from 10 to 15 years and all participants were Mexicans.

To be included in the study, participants of the patient groups had to be diagnosed with systemic lupus erythematosus with or without neuropsychiatric manifestations accordingly to ACR criteria (diagnostic criteria defined by the ACR, 1997 and ACR 1999, respectively). Diagnoses were made by a pediatric rheumatologist at Department of Pediatric Rheumatology of the Medical Unit of High Specialty, "La Raza" IMSS. The children had to be enrolled in school, to have started pharmacologic treatment (Table 1 describes medication of each patient at evaluation time besides clinical profile), to not have experienced or being in a period of depression or anxiety (evaluated with the Children's Depression Scale [CDS]; and the revised version of the scale of Manifest Anxiety [CMAS-R]; respectively), and to not have presented with lupus outbreaks in the six months prior to the study. Participants were excluded if they had an IQ of less than 70 and if, prior to an SLE or NPSLE diagnosis, they were diagnosed with some form of neurological disease.

Interview

The neuropsychological evaluation was carried out in a conditioned office, which had the spatial requirements for the neuropsychological tests. To gather data about the patients and the course of their illnesses, an initial interview was carried out in which personal information was gathered, such as aspects of their childhood development, demographic characteristics and education (Table 1). Children came from families with similar demographic characteristics and working class parents. The parents of the patients signed an informed consent form accepting the neuropsychological evaluation for their children and participation in our study. The research was approved by the Institutional Ethical Committee (FES-I, UNAM) and all procedures followed the ethical standards of the National Committee on Human Research (NOM 41bis, NOM-012-SSA3-2012) and the Declaration of Helsinki 1975, in its subsequent revisions.

Instruments

Given that some of the tests in the battery to evaluate cognitive functions in patients with SLE proposed by ACR do not have defined standards for the Mexican population, a battery that evaluates the cognitive areas established by the ACR [8] was adapted for those affected with SLE and NPSLE in this study by using tests that have standards defined for the Mexican population. The neuropsychological battery was build up with subtest of two inventories:

- Wechsler Test for Children (WISC-IV) [18]
- Neuropsychological Assessment for Children (NAC) [19]

Procedure

Neuropsychological assessment was applied by a trained neuropsychology master. Children diagnosed with SLE or NPSLE who met the inclusion criteria were evaluated, this evaluation was performed over two 1.5 to 2 h sessions. In the first session, parents filled out the information questionnaire and signed the consent form allowing the children to be evaluated with the WISC-IV in that session. Parents were also asked to fill up the CDS and the CMAS-R at home. In the second session the children were evaluated with the NAC. Once both neuropsychological evaluations were completed, scores were obtained for each of the subtests and statistical analyses were performed.

To perform the neuropsychological analysis, the normalized scores for each subtest were obtained. For the subtests of the WISC-IV and of the NAC, the scaled score was evaluated by the following established parameters: <7 were considered significantly below normal; from 7 to 13 was considered normal; and >13 were considered significantly above normal.

A detailed analysis of cognitive performance was developed for each patient and for each patient group, allowing us to obtain information on which of the cognitive areas reached average or above-average performance and which ones reached substandard or below-average performance. With this information, it was determined how frequently

Lupus	**NPSLE patients**							**SLE patients**			
Patients	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Age	14	10	15	14	11	10	11	14	15	14	11
Gender	F	F	M	F	F	F	F	F	M	F	F
Age of diagnosis	NA	7	NA	9	9	7	6	11	11	11	9
Evolution time	NA	2	NA	5	2	3	5	3	4	4	2
Systemic affection	NA	HM MCA RM	NA	CM AM	RM AM	HM AM	RM HM	RM AM HM	MCA AM RM(IIB)	RM MCA HM AM	RM MCA HM
Serologic findings	NA	APS	NA	NA	ANA anti DNA	APS	ANA Anti-DNA	ANA, Anti-DNA	NA	ANA Anti-DNA	ANA Anti-DNA
MRI	NA	Normal	Normal	NA	Normal	Normal	NA	Normal	NA	NA	Normal
SPECT	Normal	Normal	NA	Hypoperfusion Left Parietal Ischemic Vascular disease	Hypoperfusion Right Occipital lobe Vasculitis	Normal	Normal	Hypoperfusion Left Parietal lobe	Normal	NA	Normal
Treatment	NA	PDN MMF AZA calcium	NA	MMF	PDN Captopril MMF calcium	PDN MMF calcium Captopril	MMF AZA	PDN MMF Captopril	PDN MMF calcium Chloroquine	MMF AZA Captopril	PDNCaptopril calcium

Abbreviations: ACM: Atypical Cutaneous Manifestations; AM: Articular Manifestations; ANA: Anti-Nuclear Antibodies; Anti-DNA: Anti-DNA Antibodies; APS: Antiphospholipid Syndrome; APA: Antiphospholipid Antibodies; AZA: Azathioprine; CM: Cutaneous Manifestations; HM: Hematological Manifestations; MCA: Middle Cerebral Artery Occlusion; MMF: Mycophenolate Mofetil; MRI: Magnetic Resonance Imaging; NA: Not Available; PDN: Prednisone; RM: Renal Manifestations; SPECT: Single-Photon Emission Computed Tomography

Table 1: Demographic and clinical characteristics of the SLE and NPSLE groups.

patients in each group performed below-average on the tests despite the absence of statistically significant differences between the groups.

The analysis also allowed us to determine the number of cognitive areas affected in each patient in order to classify the level of cognitive impairment presented.

Statistical analysis

To determine if there were differences in cognitive performance between patients with SLE, patients with NPSLE and control children, One Way Analysis of Variance (ANOVA) was performed to compare IQ; the Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed Indexes of the WISC-IV. Also ANOVA was used to compare the score of each subtest of the 7 cognitive domains assessed with NAC and WISC-IV. Multiple comparisons were carried out with the Holm-Sidak or Dunns method. If data distribution did not follow normal (Gaussian) distribution, Kruskall Wallis non parametric test was used instead. The statistical software of Sigma Plot 12.0© was used for the analysis and confidence interval was 95%, and statistical significance of $p<0.05$ was set.

Results

Comparing total IQ with the WISC-IV among groups showed that NPSLE patients exhibited significant differences compared to control children, but no with SLE patients; however SLE patients did not exhibit difference with control children (Figure 1A). Verbal comprehension index in both NPSLE and SLE patients exhibited significant difference compared to control, while working memory index and processing speed index, differences were exhibited only between NPLS patients and control children. Group did not show differences in the perceptual reasoning index (Figure 1A).

The analysis to determine if there were variations among the groups in any of the WISC-IV subtests showed significant differences in Block Design (NPSLE *vs.* Control and SLE *vs.* Control), Vocabulary (differences were between NPSLE *vs.* Control and Control *vs.* SLE) and Comprehension (differences were found between NPSLE vs. Control and SLE vs. Control) subtests scales. No changes were found between NPSLE and SLE patients. The performance in the Letter-Number Sequencing subtest showed significant differences between NPSLE versus Control Group, as well as, in Cancellation and Information subtest, but there were no differences between NPSLE and SLE patients groups, Figure 1B).

NAC evaluations are illustrated in Figure 2; NPLSE patients exhibited significant difference compared to control children in the performance of the Memory subtest: Complex Figure Coding, Complex Figure Recall, Figure List Recall and Figure Clues; In the Visuospatial Abilities subtest: Follow Instructions Right-left, Express Instructions right-left; and in the Executive functioning subtest: Correct Models Design with minimal movements and Number of Movements.

SLE patients exhibited differences compared to control group in the execution of the Attention subtest: Digit span forward and Digit Span Backward; In the Memory subtest: Word List Coding; In the Visuospatial Abilities subtest: Line Orientation; In the Language subtest: Denomination; and in the Executive functioning subtest: Correct Models Design.

Both groups of patients exhibited differences in their performance compared to control group in the Memory subtest: Figure List Coding and Figure List Recall; and in the Visuospatial Abilities subtest: Location Points.

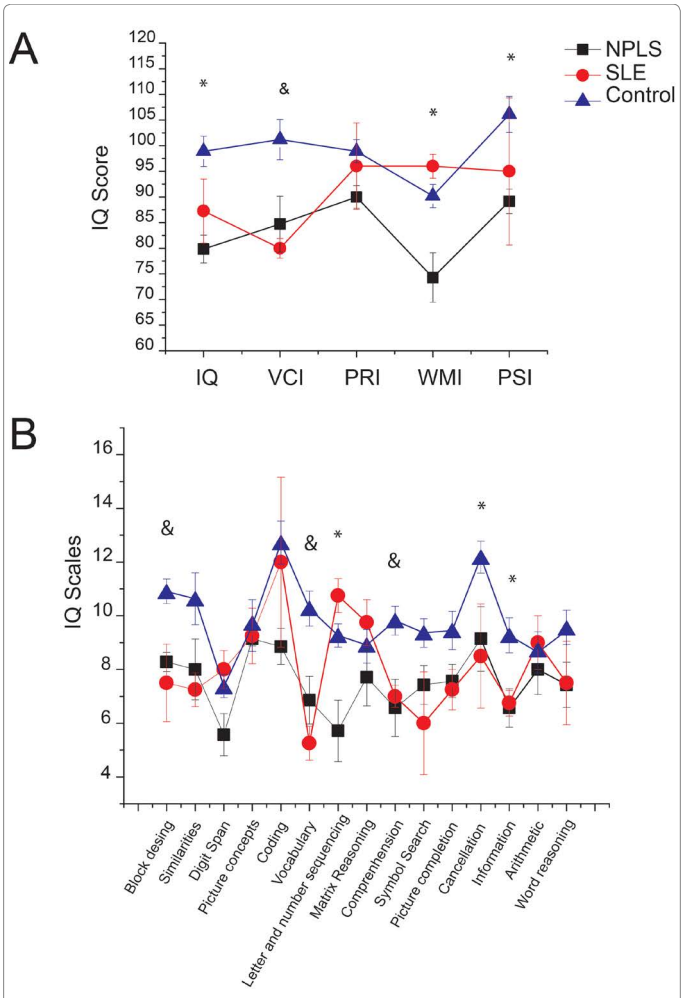
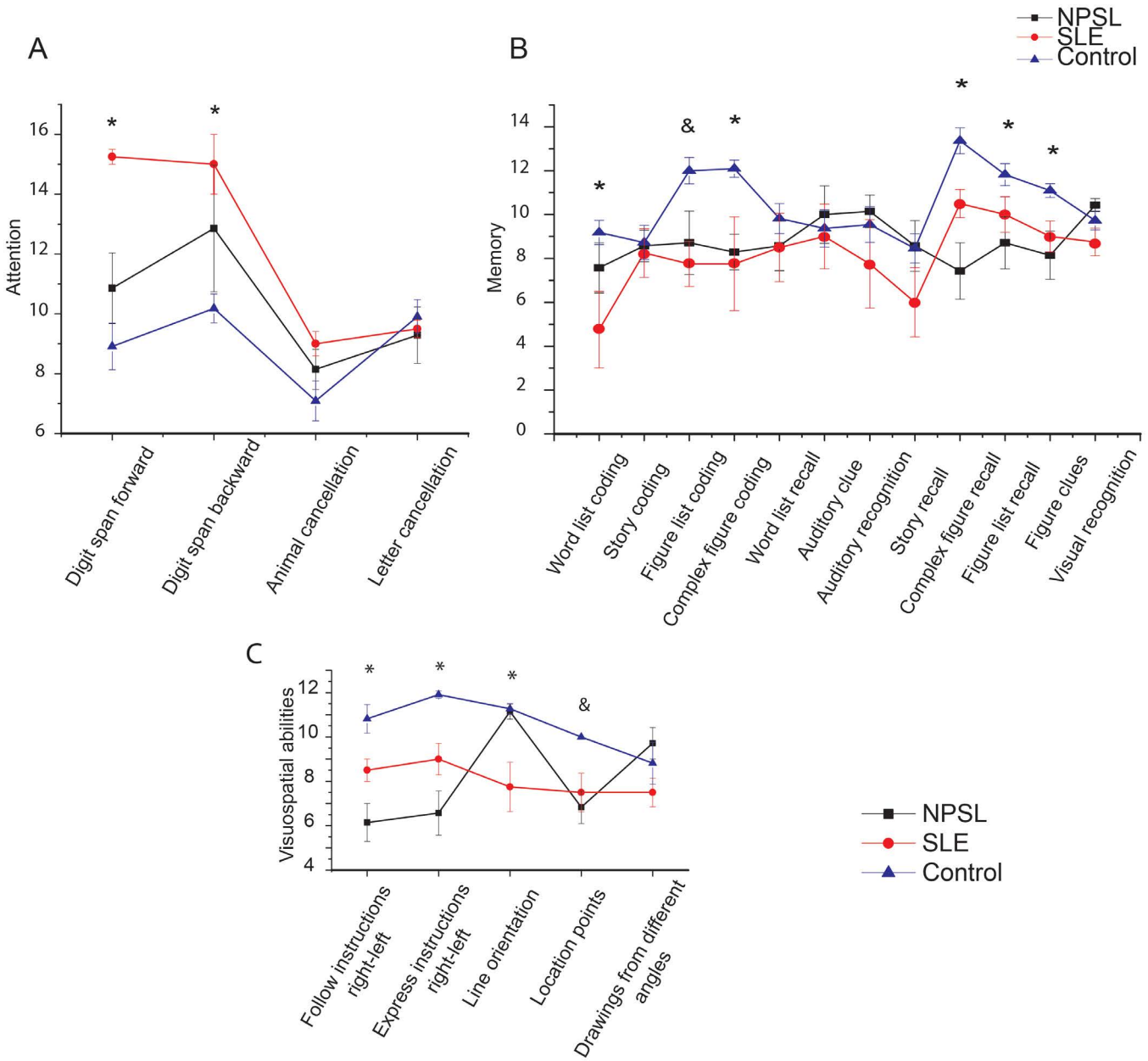


Figure 1: Cognitive profile obtained with WISC-IV scores.
A) IQ: Intelligence Quotient ($F_{2,19}$=8.767, p=0.002, NPSL *vs.* control); VCI: Verbal Comprehension Index (VCI, $F_{2,19}$=5.982, p=0.010, NPSL *vs.* control); PRI: Perceptual Reasoning Index; WMI: Working Memory Index ($F_{2,19}$=9.233, p=0.002, NPSL *vs.* control); PSI: Processing Speed Index (H_2=7.466, p=0.024 NPSL *vs.* Control). The NPSLE group exhibited significantly more deficits in the WISC-IV Indexes than the SLE patients, which did not differ from control subject except in the Verbal Index.
B) WISC-IV subtest scores. WISC-IV subtests showed significant differences in **Block Design** ($F_{2,19}$=7.21, p=0.005; NPSLE *vs.* Control, t=2.972, p=0.008; and SLE *vs.* Control, t=3.198, p=0.009), **Vocabulary** ($F_{2,19}$=9.188; p=0.002; NPSLE *vs.* Control, t=3.114, p=0.006; and Control *vs.* SLE, t=3.792, p=0.002), **Comprehension** ($F_{2,19}$=5.395, p=0.014; NPLS vs. Control, t=3.030, p=0.014; and SLE vs. Control, t=2.178, p=0.042), **Letter-Number Sequencing** ($F_{2,19}$=8.511, p=0.002; NPSLE *vs.* Control, t=3.375, p=0.006), **Cancellation** ($F_{2,19}$=3.617, p=0.047; NPSLE *vs.* Control, t=2.183, p=0.042) and **Information** ($F_{2,19}$=4.29; p=0.029; NPSLE *vs.* Control, t=2.647, p=0.032) subtests scales. There were no differences between NPSLE and SLE patients groups.
& significant differences between SLE and NPSLE with the control group (Holm-Sidak method for multiple comparisons)
***** Significant differences between NPSLE with the control group (Holm-Sidak method for multiple comparisons)

Accordingly to ACR diagnostic criteria, to determine cognitive impairment the score obtained in the evaluation needs to be two or more standard deviations (SD) below the mean in key domains; while cognitive decline is defined as a score 1.5-1.9 SD below the mean (Ad Hoc Committee on Lupus Response Criteria, 2007). Cognitive impairment is considered focal if one of more measures within one domain is affected and multifocal when two or more domains are


A
B
C
NPSL
SLE
Control
Attention
Memory
Visuospatial abilities
Digit span forward
Digit span backward
Animal cancellation
Letter cancellation
Word list coding
Story coding
Figure list coding
Complex figure coding
Word list recall
Auditory clue
Auditory recognition
Story recall
Complex figure recall
Figure list recall
Figure clues
Visual recognition
Follow instructions right-left
Express instructions right-left
Line orientation
Location points
Drawings from different angles

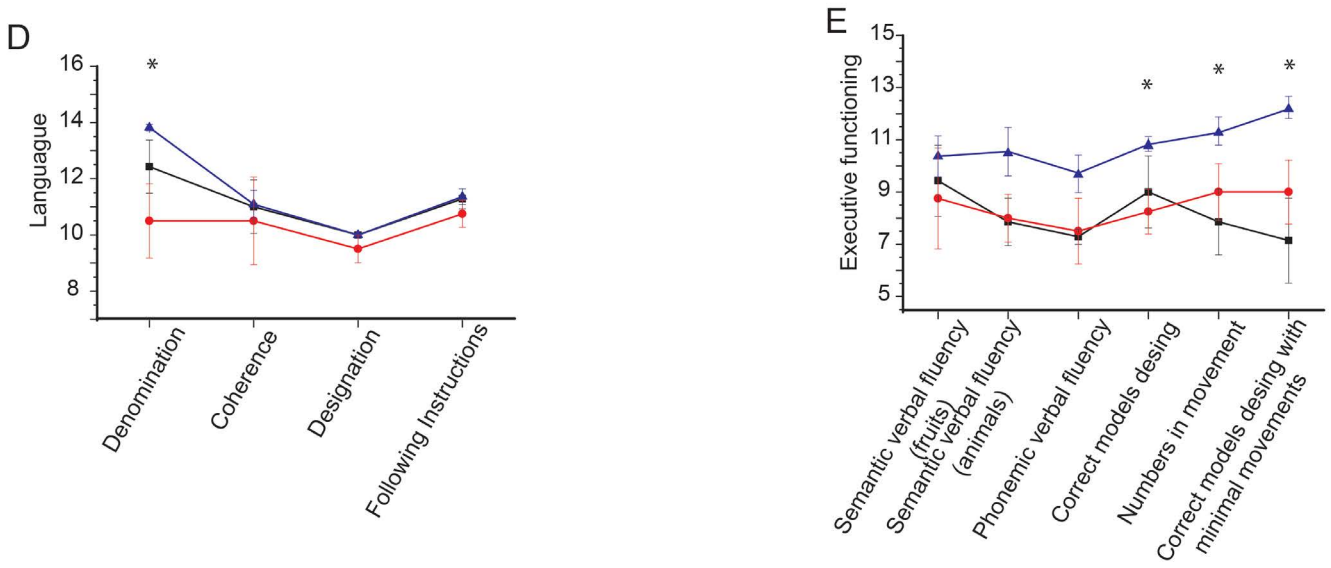


Figure 2: NAC scores A) memory, b) attention, c) visuospatial abilities, d) language, e) executive functioning.
A) **Memory:** NPLSE patients *vs.* control children exhibited significant difference in **Complex Figure Coding** (H_2=10.711, p=0.005, Q=2.860, p<0.05); **Complex Figure Recall** ($F_{2,19}$=12.724 p<0.001, t=5.028, p<0.001); Figure List Recall ($F_{2,19}$=4.241, p=0.030, t=2.870, p=0.029); **Figure Clues** (H_2=8.67, p=0.013, Q=2.482, p<0.05) subtests. SLE patients' *vs.* control group exhibited differences in **Word List Coding** ($F_{2, 19}$=3.803, p=0.041, t=2.737, p=0.039) subtest. NPLS and SLE patients exhibited differences with control children in **Figure List Coding** ($F_{2,19}$=5.089, p=0.017, t=2.680, p=0.044 control vs. SLE and t=2.502, p=0.043 control *vs.* NPSLE); **Figure List Recall** ($F_{2,19}$=4.241, p=0.030, control vs. NPLS, t=2.870, p=0.029) memory subtests.
B) **Attention Only** SLE patients *vs.* control group exhibited differences in the **Digit span forward** (H_2=11.087, p=0.004, Q=3.258, p<0.05); **Digit Span Backward** (H_2=7.588, p=0.023, Q=2.560, p<0.05).
C) Visuospatial Abilities subtest: NPLSE patients *vs.* control children exhibited significant difference in **Follow Instructions Right-left** ($F_{2,19}$=11.272, p<0.001, t=4.728, p<0.001); **Express Instructions right-left** (H_2=17.378, p<0.001, Q=3.890, p<0.05). SLE patients *vs.* control group exhibited differences in the **Line Orientation** (H_2=6.727, p=0.035, Q=2.416, p<0.05). NPLS and SLE *vs.* patients exhibited differences against control children in **Location Points** (H_2=18.441, p<0.001, control *vs.* SLE; Q=2.638, p<0.05; and control *vs.* NPLS Q=3.686, p<0.05) subtest.
D) **Language** SLE patients exhibited differences compared to control group in **Denomination** (H_2=10.137, p=0.006, Q=2.823, p<0.05) subtest.
E) **Executive functioning subtest**: NPLSE patients *vs.* control children exhibited differences in the performance **Correct Models Design with minimal movements** (H_2=10.313, p=0.006, Q=2.914, p<0.05); **Number of Movements** ($F_{2, 19}$=4.146, p=0.032, t=2.799, p=0.034). SLE patients exhibited differences compared to control group in the execution of Correct Models Design (H_2=9.077, p=0.011, Q=2.650, p<0.05) subtest.
One way ANOVA, and Holm-Sidak method for multiple comparisons was used for parametric distribution or Kruskall Wallis, ANOVA on Ranks and Dunn's method for multiple comparisons for non-parametric distribution
& Significant differences between SLE and NPSLE with the control group
***** Significant differences between NPSLE with the control group

affected. Table 2 shows the percentage of patients, with NPSLE and SLE, whose performance was between 1.5 or 2 SD below the mean in each of the seven cognitive domains proposed by ACR, corresponding to a cognitive decline or cognitive impairment respectively.

Attention domain was assessed by Cancellation Letters and Drawings Cancellation tasks, no patients presented low performance in these tasks. Memory domain included Coding, Delayed free recall and Delayed cued recall tasks. Regarding to coding a Figures Set, 14% scored 2 SD below the average in the NPSL group whilst in Coding Words List, 29% of patients showed scores below 1.5 SD, while 14% of patients showed scores below 2 SD in the NPSLE group. One patient in each group had a score below 1.5 SD in coding a Story. In delayed free recall 29%, 14%, 14%, 14% of NPSLE group exhibited scores 1.5 SD in Figures set, Words list, Story and Complex Figure, respectively. In SLE group only one patient had scores below 1.5 and another one 2 SD below average in Story free recall. In Visuospatial processing one patient of NPSLE group scored below 1.5 SD in Complex Figure copy and in Location in a Map and one patient of SLE group below 2 SD in Complex Figure.

In language domain three patients of NPSLE group scored below 1.5 SD in WISC IV Vocabulary subtest. And three patients of the SLE group scored below 2 SD. No problems were founded in Images Nomination, Narrative Coherence, Point Images and Following Instructions.

In WISC IV subtests that assessed reasoning/ problem solving domain, NPSLE group exhibited at least one patient who scored below 1.5 in Arithmetic, Word Reasoning, Comprehension and Similarities and two patients scored 2 SD below mean in Matrix Reasoning and Comprehension; SLE group only had one patient who scored 1.5 SD below mean in two subtests (Block Design and Word Reasoning).

The evaluation of processing speed domain showed that both groups had patients with impairments below 1.5 SD in this area, but more patients in the SLE group showed scores below 1.5 SD.

In executive functions, some patients of NPSLE group showed problems in planning (2 SD below average) and working memory tasks (1.5 and 2 SD below the average); no problems were observed in SLE group, except a patient who scored low in Phonemic Fluency.

Main cognitive impairments in both groups were observed in memory, visuospatial processing, reasoning/problem solving, speed processing and executive functions in both groups (NPSLE and SLE), Nonetheless, these impairments were only observed in a low percentage of patients. The less impaired areas were language and selective

			NPSLE group		SLE group	
Domain	**Subdomain**	**Subtest**	**-1.5 SD % (n)**	**- 2 SD % (n)**	**-1.5 SD % (n)**	**-2 SD % (n)**
	Selective	NAC: Cancellation Letters (X)				
		NAC: Cancellation Drawings (W)				
Memory	Coding	NAC: Figures Set (AA)		14 (1)		
		NAC: Words List (Y)	29 (2)	14 (1)		50 (2)
		NAC: Story (Z)	14 (1)		25 (1)	
	Delayed free recall	NAC: Figures Set (AH)	29 (2)			
		NAC: Words List (AC)	14 (1)			
		NAC: Story (AF)	14 (1)		25 (1)	25 (1)
		NAC: Complex Figure (AG)	14 (1)	14 (1)		
	Delayed cued recall	NAC: Figures Set (AI)		14 (1)		
		NAC: Words List (AD)				
Visuospatial processing		NAC: Complex Figure (AB)	14 (1)			25 (1)
		NAC: Location in a Map (AT)	14 (1)			
		NAC: Orientation of Lines (AS)				
		NAC: Different Angles (AU)				
Language	Word knowledge	WISC-IV: Vocabulary (H)	47 (3)			75 (3)
	Expressive	NAC: Images Nomination (AL)				
		NAC: Narrative Coherence (AM)				
	Comprehensive	NAC: Point Images (AN)				
		NAC: Following Instructions (AO)				
Reasoning/ Problem solving	Arithmetic reasoning	WISC-IV: Arithmetic (P)	14 (1)			
	Nonverbal reasoning	WISC-IV: Matrix Reasoning (J)		14 (1)		
	Visuospatial reasoning	WISC-IV: Block Design (C)			25 (1)	
	Verbal reasoning	WISC-IV: Word Reasoning (Q)	29 (2)		25 (1)	
		WISC-IV: Comprehension (K)	14 (1)	14 (1)		
		WISC-IV: Similarities (D)	14 (1)			
Processing speed		WISC-IV: Symbol Search (L)	14 (1)		25 (1)	25 (1)
		WISV-IV: Coding (G)			25 (1)	
		WISC-IV: Cancellation (N)	14 (1)		25 (1)	
Executive Functions	Semantic fluency	NAC: Semantic fluency (animals) (AX)				
	Phonemic fluency	NAC: Phonemic fluency (letters) (AY)			25 (1)	
	Planning	NAC: México Pyramid (BB)		29 (2)		
	Working memory	WISC-IV: Letter-Number Sequencing (G)	14 (1)	14 (1)		
		WISC-IV: Digit Span (E)	29 (2)	14 (1)		

Table 2: Neuropsychological assessment instruments used in pediatric patients with SLE and NPSLE to cover the seven cognitive domains proposed by ACR and percentage of patients that are distributed in two levels of performance: cognitive decline (-1.5 SD) and cognitive impairment (-2 SD).

attention.

The analysis of the number of domains affected on a patient-by-patient basis, allows us to establish the level of neuropsychological impairment of each patient and to determine if the cognitive impairment was focal or multifocal according to ACR criteria. Table 3 shows individual performance of patients with SLE and NPSLE in the different cognitive domains proposed by the ACR. The majority of patients of both groups showed a level of dysfunction that can be considered as cognitive decline (1.5 SD below the mean); there were few cases in which cognitive impairment was observed (2 SD below the mean). On the other hand, we found that patients of both groups showed a similar multifocal dysfunction pattern, defined as disability in multiple domains. Also we can observe in Table 3 a patient (6) in the NPSLE group who did not have any dysfunction.

Discussion

The aim of the present study was to determine if there are differences between pediatric patients diagnosed with SLE versus those diagnosed with NPSLE in any of the 7 cognitive areas recommended by the ACR.

The results in this study indicate that there were not important cognitive differences between children with SLE and those with NPSLE. In general, both clinical groups performed worse than healthy controls, but NPSLE patients were more cognitive impaired compared with healthy controls and with normative data of the tests employed.

In the comparison with control subjects, there were important differences with NPSLE patients in IQ and Working Memory and Processing Speed Indexes of WISC IV. In Verbal Comprehension, both samples had scores below the control group. When specific subtests were analyzed differences were observed between both clinical groups and the control group in Block Design, Vocabulary and Comprehension; and between NPSLE and the control group in Letter and Number Sequencing, Cancellation and Information. These results are similar to those reported in a literature review where pediatric SLE samples had cognitive impairment related with complex problem solving, working memory, verbal memory, attention and visuomotor integration [3]. Low scores observed in our SLE and NPSLE samples in verbal tasks

			NPSLE patients							SLE patients			
Domain	**Subdomain**	**Subtest**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Attention	Selective	NAC: Cancellation Letters (X)											
		NAC: Cancellation Drawings (W)											
Memory	Coding	NAC: Figures Set (AA)		2									
		NAC: Words List (Y)			1.5	1.5			2				2
		NAC: Story (Z)			1.5							1.5	
	Delayed free recall	NAC: Figures Set (AH)		1.5					1.5				
		NAC: Words List (AC)				1.5							
		NAC: Story (AF)			1.5					1.5	2		
		NAC: Complex Figure (AG)		2			1.5						
	Delayed cued recall	NAC: Figures Set (AI)							2				
		NAC: Words List (AD)											
Visuospatial processing		NAC: Complex Figure (AB)	1.5										2
		NAC: Location in a Map (AT)		1.5									
		NAC: Orientation of Lines (AS)											
		NAC: Different Angles (AU)											
Language	Word knowledge	WISC-IV: Vocabulary (H)			1.5		1.5		1.5		1.5	1.5	1.5
	Expressive	NAC: Images Nomination (AL)											
		NAC: Narrative Coherence (AM)											
	Comprehensive	NAC: Point Images (AN)											
		NAC: Following Instructions (AO)											
Reasoning/Problem solving	Arithmetic reasoning	WISC-IV: Arithmetic (P)		1.5									
	Nonverbal reasoning	WISC-IV: Matrix Reasoning (J)	2										
	Visuospatial reasoning	WISC-IV: Block Design (C)											1.5
	Verbal reasoning	WISC-IV: Word Reasoning (Q)	1.5				1.5						1.5
		WISC-IV: Comprehension (K)				1.5	2						
		WISC-IV: Similarities (D)	1.5										
Processing speed		WISC-IV: Symbol Search (L)					1.5				2		1.5
		WISV-IV: Coding (G)									1.5		
		WISC-IV: Cancellation (N)											
Executive Functions	Semantic fluency	NAC: Semantic fluency (animals) (AX)	1.5							1.5			
	Phonemic fluency	NAC: Phonemic fluency (letters) (AY)									1.5		
	Planning	NAC: México Pyramid (BB)	2				2						
	Working memory	WISC-IV: Letter-Number Sequencing (G)	2	1.5			2						
		WISC-IV: Digit Span (E)	2		1.5	1.5							

Table 3: Individual performance of patients with SLE and NPSLE in the seven cognitive domains proposed by the ACR.

as vocabulary and comprehension were not mentioned as deficient in that review.

In domains proposed by the ACR as attention, memory, language, visuospatial abilities and executive functions, assessed with NAC and WISC IV subtests, there were differences between NPSLE and control group in several tasks. In attention domain, patients showed less attention span and in visuospatial domain had troubles with right-left instructions, lines orientation and location on a plane. This finding appears to confirm a pattern of visuospatial deficits and attention problems reported in children and adults with SLE [3,20].

In memory domain the NPSLE patients showed deficits in coding and recall processes, in both visual and verbal modalities. This result is partially consistent with Levy et al. review [3] who reported deficits in visual memory. Memory impairments suggest temporal medial and frontal anomalies. The NPSLE patients performed poorly on measures of executive functions, they had difficulties in solving problems and reduced span of working memory, but fluency was normal, such deficits are similar to previous reports in children [3,7]. Executive functions are related with integrity of fronto-striato-thalamic circuits [21]. Within the verbal domain, NPSLE patients performed poorly than control healthy group on verbal tests as naming, vocabulary and verbal comprehension.

In the last two measures also SLE children had worse performances than control group. These verbal deficiencies in general are not reported in literature and we can consider this a contribution of the present work; temporal and frontal areas are related with comprehension and verbal expression. The pattern of cognitive decline in SLE and NPSLE samples studied was heterogeneous and it was not limited to tasks that include processing speed, so it does not conform to the pattern of sub cortical damage that has been proposed for this pathology [22], but rather cortical and sub cortical components are revealed as Rains [23] as well as, Sarbu et al. [11] proposed.

Additionally to the comparison of groups, we analyze the percentage of patients who performed 1.5 and 2 SD below the average of the normative data of the tests employed, in these, as many as 30% of patients of both groups had scores below these reference points. Also in individual performance related to normative data some patients showed scores below age-matched norms in many subtests, although one patient had no low scores. According to ACR criteria, these findings indicate cognitive decline rather than impairment (being necessary for the latter to have scores below two SD), and in the majority of analyzed cases cognitive decline is multifocal being more than one affected domain.

A similar description of children with LES was made by Muscal et al. [24] who found that scores below 1.5 SD were common in early phases of the disease. Furthermore, they found white matter lesions and cerebral and cerebellar volume loss in his patients but don't correlate this finding with neuropsychological results. In our case we did not have neuroimaging studies available in all cases and those we had were normal (Table 1), so we could not establish the association between structural changes and neurocognitive decline or impairment. These authors reported that 59% of children and adolescents with SLE developed impairments. This percentage is higher than what we found in our sample and in both were investigated samples of patients at initial stages of the disease.

The exact mechanism of the pathogenesis of cognitive changes in patients with Lupus is still unknown, several authors have reported that antibodies and cytokines are responsible [25,26], partaking in the damage to the CNS via thrombosis, vasculopathies, inflammation and neural death [27]. In our sample only two of NPSLE and one of SLE patients exhibited hypoperfusion, but the MRI was normal or no available in the rest of patients, medication received was supposed to ameliorate symptoms [28], which deferred in each patient and did not allow standardizing a therapeutic approach.

Cognitive injury in patients with SLE who lack psychiatric symptoms has typically been attributed to subcortical dysfunction, white matter lesions, and hydrocephalus [22,29,30], although cortical anomalies have been reported as well [24,29]. As described above, patients with SLE who lack psychiatric manifestations already present CNS structural lesions, despite a general lack of clinical data on these changes [11,31].

Conti et al. [26] evaluated patients with SLE and NPSLE in 5 cognitive domains (attention, memory, abstraction, executive function and visuospatial abilities) to explore frontal-subcortical pathways and found that the most compromised cognitive domain was visuospatial abilities; supporting that this pathway is impaired in both group of patients. Benedict et al. [32] have established that the cognitive deficit in patients with SLE has a subcortical pattern closer to that seen in Huntington's disease than the cortical pattern seen in Alzheimer's disease [22]. However, cognitive profile in SLE can be also closer to that of multiple sclerosis and that those impairments are cortical in nature [32]. It should be noted that the existence of subcortical pathologies does not rule out the presence of cortical impairments [11,23].

In our evaluations, both groups of patients show impairments in the same areas; however, the NPSLE group manifests more frontal impairments compared to the SLE group, although this does not imply that the latter group itself is not free of impairments. It should be emphasized that in attention-based tasks, the NPSLE group was the only one that presented difficulties; however its performance is similar to control children. Additionally, in working memory tasks, that group performed significantly worse than the SLE group and in the problem planning and solving tasks, the NPSLE group took longer in developing a suitable strategy to solve the tasks. From this, it is inferred that frontal-cortical impairments exist in the NPSLE group.

Even though has been reported that abnormalities in NPSLE are more diffuse and heterogeneous [3,33] finding cognitive impairments in patients with NPSLE was expected, because their initial symptoms involved some sort of neurological or psychiatric compromise; in contrast, initial symptoms of patients with SLE tended to be renal and cutaneous impairments. However, both groups ended up demonstrating cognitive impairments in our study.

The ACR has established that the diagnostic criterion that distinguishes SLE from NPSLE is cognitive deterioration; according to the results of the present study and those reported by Muscal et al. [24], it is possible that cognitive impairments are not exclusive to those who have already presented with some type of neurologic or psychiatric syndrome like NPSLE patients but also in children with SLE. On completing the patient-by-patient analysis to determine what level of cognitive deterioration they possess, it was found that almost all patients with NPSLE presented with mild deterioration, that is, they presented with one to three affected cognitive areas. In contrast, half of the patients with SLE presented with mild deterioration, and the other half presented with severe deterioration, showing impairments in five or more cognitive areas, this data has not been described before in the literature. In the group of patients with SLE, two subjects were found who had low scores in five or more domains, pointing to severe cognitive deterioration. We cannot rule out that some of the cognitive deterioration should be due to a combination of disease and medication side effects in SLE patients.

Conclusion

Based on the above, one might infer that there might be some stability in the cognitive deterioration of patients who first show neurologic or psychiatric symptoms; as our study shows, SLE patients display cognitive abnormalities, but a diagnosis of NPSLE results in patients receiving treatment to ameliorate neurological problems, which improved cognitive functioning in a way that makes their deficit not as severe as it is for patients with SLE.

The life expectancy for patients with SLE has enhanced drastically in recent decades [1], therefore, it is important to consider that children with SLE may present with cognitive damage and that having received the diagnosis of SLE at an early age could have an effect on their prognosis. It is recommended that when a child is newly diagnosed with SLE, a neuropsychological battery should be administered to determine if any type of cognitive abnormality might already exist and thus, intervention strategies can be developed to compensate for the cognitive deficits that will surely arise during the course of the disease.

Limitations of the Study

Because patients were referred with specific limits on aspects such as age, date of first clinical manifestations, and types of clinical manifestations, the sample was limited to 12 patients afflicted by Lupus, which is not really sufficient to generalize the data to the entire population. Additionally, the two groups were not balanced in their number of patients who already presented with neuropsychiatric abnormalities. The lack of alterations in imaging studies make it difficult to correlate patients performance with the psychopathological findings, studies in the future should cover other type of evaluations like transcranial stimulation to correlate neuropsychological performance with changes in cortical excitability and synaptic plasticity in patients affected by Lupus [34].

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Ethical Approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Informed Consent

Informed consent was obtained from all patients for being included in the study.

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